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STAPHYLOCOCCIC EMPYEMA

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A thoracic empyema is more than a collection of pus in the pleural space; it is an actual abscess. The inflamed pleurae form its walls, and it is commonly divided by bands and adhesions into subspaces with little apparent intercommunication. It usually develops by lymphatic bacterial drainage into an initially sterile pleural effusion, by direct extension from the lung itself, by rupture of a subpleural abscess, by septic embolization, or by traumatic or iatrogenic contamination. For rapid and complete healing the abscess must be completely evacuated. Antibiotics must be used with pinpoint accuracy, or a chronically ill patient will come to harbor an organism resistant to all usual antibiotics. These principles are illustrated by ten case reports.

WHILE MOST physicians ascribe to the treatment of purulent collections, such as a pelvic or subdiaphragmatic abscess, by surgical drainage, many apparently do not consider an acute empyema in the same light.[1] There are, perhaps, logical reasons for this attitude. Empyema is usually a complication of an antecedent illness; it is insidious in onset, and the diagnosis is frequently overlooked. When diagnosed, it can be readily followed by roentgenographic examination and most often appears accessible to thoracentesis and local therapy. With this in mind, many physicians will perform repeated aspirations and local instillation of antibiotics, which may be successful, although therapy is thereby prolonged and potentially dangerous. More insidious, however, is the false assumption that all acute empyemas may be treated in this manner, particularly those of staphylococcic origin.

An empyema is more than a purulent collection in the pleural space. It constitutes an actual abscess, and the pleurae, formerly thin and glistening, are now abscess walls—thickened, granular, inflamed, and supporting a pyogenic growth. In addition, the pleural space, in reaction, develops bands of fibrous tissue which make tortuous and sinuous extensions with little apparent communication between the different partitions. To assume that daily aspirations of a small amount of pus will empty this space is wistful thinking. For rapid and complete healing, the abscess must be completely evacuated,

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the partitions separated, and the space obliterated. Failure to perform this will result in a functionless, trapped, compressed lung, and more extensive surgical treatment will be needed for reexpansion of the lung and cure of the empyema.

Although some cases of acute staphylococcic empyema, if treated early, will respond to thoracentesis, local instillation of antibiotics, and enzymatic débridement,[2] to prescribe this as the preferred treatment is dangerous. Actually, many patients whose disease responds to thoracentesis and antibiotic therapy have infected effusions without true abscess formation. The empyema may be aborted but not cured, since it has never existed. For the most part, pinpoint accuracy of the antibiotic is the key factor,[3] and, in combating the staphylococcus, this has been only temporarily achieved when a new antibiotic is introduced. When resistance develops, conservative treatment again results in a prolonged period of multiple inadequate attempts of thoracentesis with eventual failure; the chronically ill patient now harbors an organism resistant to all antibiotics, well past the optimum time for the most effective and simple surgical drainage.

The following case reports, collected in the past two years at the District of Columbia General Hospital and the George Washington University Hospital, are presented to illustrate this problem and to reemphasize the necessity of early surgical drainage when dealing with staphylococcic empyema.

Report of Cases

Case 1.—A 40-year-old woman was admitted to the District of Columbia General Hospital on Oct. 22, 1956. The patient, a known alcoholic and epileptic, had a three-week history of cough, chills, fever, and bilateral pleuritic pain. Physical examination revealed a blood pressure of 120/70 mm. Hg, a pulse rate of 104 per minute, a respiration rate of 48 per minute, and a temperature of 104 F (40 C). There were moist rales bilaterally with dulness to percussion and decreased breath sounds in both lung bases. X-ray examination showed a right lower lobe pneumonia with a small pleural effusion. The sputum was collected for smear and culture, and the patient was given tetracycline (Achromycin), 500 mg. intramuscularly every six hours. Despite clinical improvement, the pleural effusion increased and thoracentesis three days after admission was productive of 600 cc. of a cloudy fluid, which was subsequently found to be negative on culture. The temperature rose during tetracycline therapy, and fluid subsequently drawn by thoracentesis was positive on culture for Staphylococcus pyogenes var. aureus, coagulase positive. Erythromycin was then given, 500 mg. four times daily. Multiple thoracenteses with streptokinase-streptodornase (Varidase) instillations proved unsuccessful. Surgical drainage was performed on Nov. 15, 1956, with prompt remission of the fever and a satisfactory result.

Case 2.—A 66-year-old woman was admitted to the District of Columbia General Hospital on Feb. 1, 1956, because of a productive cough, fever, dyspnea, and general malaise of six months' duration. Studies on the medical service established the presence of a massive left pleural effusion and pneumonia. Sputum examination showed many pneumococci, and the patient was given novobiocin (Albamycin), 500 mg. every six hours. After one week no improvement was demonstrable, and antibiotic therapy was changed to that with erythromycin and then in four days to that with tetracycline, 500 mg. every six hours. Multiple thoracenteses were productive of small amounts of purulent material. After one month, no improvement was seen and open drainage was instituted. Cultures of the fluid at this time were positive for Staph. pyogenes var. aureus, coagulase positive. Nine days after drainage, the temperature was normal and the antibiotic therapy was discontinued. After prolonged treatment with irrigations, the patient made an uneventful recovery.

Case 3.—A 53-year-old woman was admitted to George Washington University Hospital on Aug. 12, 1956, because of persistent fever, chest pain on the right, and a 20-lb. (9.1-kg.) weight loss after an episode of pneumonia two months previously. At that time, she was given a diagnosis of right lower lobe pneumonia and therapy with chloramphenicol (Chloromycetin), 250 mg. every four hours, and 500 mg. of tetracycline given intravenously daily for four days was instituted. Sputum cultures revealed hemolytic streptococcus, Staph. pyogenes var. aureus, and Proteus vulgaris. Therapy with the above antibiotics was discontinued, and that with penicillin, 300,000 units every four hours, and streptomycin, 0.5 Gm. twice daily, was started, after cultures were reported moderately sensitive to these drugs. The patient was discharged from the hospital after two weeks of this therapy.

On subsequent admission to the George Washington University Hospital, examination confirmed the presence of an empyema of the right pleura. The patient was operated on under local anesthesia; a modified Eloesser flap was performed with resection at part of the sixth and seventh ribs at the posterior axillary line. A copious amount of purulent material was removed which, on culture, grew Staph. pyogenes var. aureus, coagulase positive, resistant to all the commonly used antibiotics. She was therefore not given antibiotics, but irrigation with saline solution for mechanical débridement was done frequently. After one week, the empyema cavity measured 55 cc. and she was discharged with the drainage tube in place. She continued to receive treatment at home until the space measured 10 cc. in volume, when the tube was removed. Her total period of drainage was almost four months.

Case 4.—A 16-month-old child was admitted to the District of Columbia Hospital on Feb. 17, 1957, in acute respiratory distress, breathing 48 times a minute, with a temperature of 105 F (40.5 C) and a pulse rate of 130 per minute. The patient had an upper respiratory infection for one week, which was treated by the family doctor with one injection of penicillin. The child appeared to have nuchal rigidity, and a spinal tap was done. The fluid was normal. Roentgenographic examination showed complete obliteration of the left lung field, and thoracentesis was performed. Fifty cubic centimeters of pus was removed, a smear of which showed gram-positive cocci. Therapy with chloramphenicol, 250 mg. every six hours, was started and underwater tube drainage performed. The patient made gradual improvement, and the underwater drainage was converted to open drainage. On the 41st hospital day, he developed septicemia, with Staph. pyogenes var. aureus, coagulase positive, resistant to all antibiotics except novobiocin. The chloramphenicol therapy was discontinued, and novobiocin, 100 mg. every six hours, was given for one month. The empyema space completely resolved, and the patient was discharged on May 29, 1957.

Case 5.—A 59-year-old man was admitted to the George Washington University Hospital on July 13, 1956, because of persistent fever and left upper quadrant pain after a fall two weeks prior to admission. One year before, he had suffered a cerebrovascular accident. One month prior to admission, the patient was treated for left upper quadrant pain and fever; at that time a diagnosis of urinary infection was made, and he had a remission of his symptoms.

Examination revealed an elderly, chronically ill man with aphasia and severe rheumatoid arthritis. Temperature was 102.2 F (39 C), blood pressure 140/90 mm. Hg, respiration rate 22 per minute, and pulse rate 90 per minute. There were residuals of a hemiplegia on the right side and dry rales in the right upper and left lower regions of the chest. There was tenderness in the left upper quadrant and axillary line without guarding or muscle spasm. Laboratory examination revealed a hematocrit value of 33%, leukocyte count of 9,750 per cubic millimeter, blood urea nitrogen level of 12 mg. per 100 cc., and amylase level of 7 units per 100 cc. The urine showed many clumps of bacteria, and a culture of it was positive for Staph. pyogenes var. aureus, coagulase positive. An electrocardiogram showed nonspecific T-wave changes. An x-ray of the chest revealed a fluid level in the left lung base representing a walled-off empyema or lung abscess. Thoracentesis was productive of green, bloody, purulent material that was positive on culture for Staph. pyogenes var. aureus, coagulase positive. The patient was operated on and tube drainage with water seal suction applied. Penicillin, one million units daily, and streptomycin, 1.5 Gm. daily, were given. The clinical response was good. A few days later rib resection and Eloesser flap construction were done. Therapy with erythromycin, 200 mg. every six hours, was begun at this time, and the patient made an uneventful recovery. He was transferred to another hospital for nursing care and rehabilitation.

Case 6.—A 54-year-old woman was admitted to George Washington University Hospital on June 30, 1956, because of fever, cough, and weight loss of one month's duration. The patient was being treated for an upper respiratory infection for one month prior to admission with inadequate doses of antibiotics. She was referred for admission because of deterioration of her condition and recent pain on the right side of her chest. She had had poliomyelitis at the age of 7 years and had a residual partial paralysis of her left leg.

Chest x-ray showed complete opacity of the right lower part of the chest and homogeneous densities in the right upper part, suggesting fluid or consolidation. The left lung was clear. Thoracentesis was performed and 40 cc. of purulent material aspirated. This was positive on culture for Diplococcus pneumoniae, and penicillin, 600,000 units twice daily, was given. The organism was sensitive to all antibiotics. Surgical consultation was obtained the following day, and tube drainage was performed with the patient under local anesthesia. Posterior and anterior pockets were encountered and two tubes inserted. Approximately 1,000 cc. of pus was obtained which was positive for only Staph. pyogenes var. aureus, coagulase positive, which was sensitive to all antibiotics except penicillin. The patient was given erythromycin, 250 mg. every four hours, and was discharged 10 days after surgery. The empyema space had decreased from a 1,000-cc. volume to a 38-cc. volume in that period. She was followed in the outpatient clinic and made an uneventful recovery.

Case 7.—An 11-year-old boy was admitted to George Washington University Hospital on March 20, 1957, because of persistent fever and pain of one month's duration on the left side of the chest. The boy was hospitalized one month previously at another hospital, for similar complaints, and examination at that time revealed a temperature of 104 F (40 C), pleuritic pain on the left side of the chest, a leukocyte count of 20,000 per cubic millimeter, with 90% polymorphonuclear cells, and a diffuse haziness on x-ray of the left lung field. Thoracentesis was nonproductive, and he was given a broad-spectrum antibiotic and penicillin. His fever subsided, and, because of a strongly positive intermediate PPD test, he was discharged on therapy with streptomycin and isoniazid. Several days after discharge his temperature was again elevated, but repeated x-ray examinations showed no change and no pulmonary findings could be elicited. A histoplasmin agglutination test was recorded as 1:16 one week prior to admission, but a second test just before admission was not diagnostic.

Physical examination showed a chronically ill boy. X-ray of the chest at this time showed a circumscribed mass at the upper posterior mediastinum on the left. Findings on examination were entirely normal except for an elevated white blood cell count of 22,300 per cubic millimeter, with 56% segmented cells, 1% band cells, 41% lymphocytes, 1% monocytes, and 1% eosinophils. With the patient under local anesthesia, an empyema pocket was found by needle aspiration. Drainage required resection of a small portion of the left seventh and eighth ribs about 2 cm. lateral to the transverse process.

Over 200 cc. of foul-smelling pus was removed. This was positive on culture for Staph. pyogenes var. aureus, coagulase positive. The patient was placed on therapy with penicillin and streptomycin for five days, and with drainage he had prompt remission of his fever. He was discharged to the outpatient department in one week and was subsequently treated with frequent irrigations until the volume of the space was reduced to 5 cm. of water, when the tube was removed. The patient required no antibiotics after discharge, and the space was closed in approximately five weeks.

Case 8.—A 9-month-old boy was admitted to the District of Columbia General Hospital because of a persistent fever and pharyngitis. He was given penicillin for two days and tetracycline orally for one day as an outpatient.

Examination disclosed an acutely ill, listless infant with a temperature of 105.6 F (40.9 C) and a respiration rate of 40 per minute. The patient had minimal pharyngitis, bilateral otitis media, diffuse rhonchi throughout both lung fields with decreased breath sounds, and dulness to percussion over the right side of the chest. An x-ray the following day showed a mottled infiltration in the right lung field with pleural effusion obscuring most of the right side. Because of four loose bowel movements, the patient was placed in isolation and given fluids intravenously. Penicillin, 300,000 units every six hours, and sulfisoxazole (Gantrisin), 1 Gm. per pound of body weight administered intravenously, were given. The following day a throat culture was reported positive for Staph. pyogenes var. aureus, coagulase positive. The temperature was still elevated to 104 F (40 C), the respiratory rate was 70 per minute, and the pulse rate was 200 per minute. Intravenously given novobiocin, 100 mg. per pound of body weight for two doses and then 50 mg. per pound every six hours, was given. The fourth hospital day no improvement was noted. Thoracentesis was performed and 20 cc. of cloudy fluid removed. Novobiocin, 100 mg., and penicillin, 300,000 units, were instilled. The patient was digitalized. He then continued to have daily thoracentesis and antibiotic instillation performed without x-ray signs of improvement or clinical evidence of response. On Sept. 21, 1957, the ninth hospital day, surgical consultation was obtained and tube drainage in the seventh intercostal space at the mid-axillary line was performed. The patient became afebrile in four days, and the tube was removed in approximately one month. He showed gradual improvement, although possible cyst formation, characteristic of staphylococcic pneumonia, was noted in the lung.

Case 9.—A 12-month-old girl was admitted on Feb. 22, 1957, to the District of Columbia General Hospital for treatment of second and third degree burns of both hands accidentally inflicted at home one week prior to admission. Physical examination showed a well-developed, well-nourished child. Temperature was 100 F (37.7 C), pulse rate 140 per minute, and blood pressure 120/80 mm. Hg. There was a mucopurulent upper respiratory infection, second and third degree burns of the palmar surface of both hands with gross secondary infection, epitrochlear and axillary adenopathy, and rhonchi in both lung fields.

X-ray on the day after admission showed a right basilar pneumonia. One week later, after surgical débridement of the burns, a diagnosis of left lower lobe pneumonia was given. During this time she was being given tetracycline, 30 mg. per pound of body weight every four hours. The patient was becoming tachypneic, and x-ray showed opacification of the entire left lung with mediastinal shift to the right. On March 10, 1956, her 10th hospital day, she became comatose. Thoracentesis was performed and 70 cc. of pus removed. Medical consultation was obtained, and repeated thoracentesis and instillation of erythromycin, 60 mg. four times a day, was advised.

Culture of the fluid obtained on thoracentesis was positive for Staph. pyogenes var. aureus, coagulase positive. Multiple thoracenteses were performed for the next 10 days with some resolution in her fever but with no significant x-ray evidence of improvement. Surgical consultation was obtained, and on March 20, 1957, surgical drainage and Eloesser flap formation were performed in the left eighth intercostal space at the left mid-axillary line. She was given chloramphenicol in addition to the erythromycin, and she showed gradual improvement until her discharge on June 16, 1957.

Case 10.—A 50-year-old man, a chronic alcoholic, was admitted to the District of Columbia General Hospital on April 1, 1956, because of pleuritic pain on the left, cough, and fever of one week's duration. Physical examination showed temperature 102.6 F (39.3 C), blood pressure 142/90 mm. Hg, pulse rate 108 per minute, and respiration rate 22 per minute. The patient had decreased breath sounds, dulness to percussion, and increased tactile and vocal fremitus over the left upper part of the chest. X-ray examination showed a left pleural effusion obscuring the lung field. Gram-positive cocci were found in the sputum, and the patient was started on a regimen of multiple thoracentesis with locally and parenterally given penicillin. Culture of the pleural fluid on April 24, 1956, was positive for Staph. pyogenes var aureus, coagulase positive. The patient was then started on therapy with erythromycin, 500 mg. every six hours, but showed no improvement; he was subsequently given chloramphenicol, 1 Gm. every six hours. On May 11, 1956, the 40th hospital day, surgical drainage was instituted, and the patient showed rapid improvement. The tube was removed on June 7, 1956, although the empyema space was not measured at the time. Three weeks later the patient showed a recurrence of his empyema, and a study with use of iodized oil (Lipiodol) revealed a space measuring 30 cc. Accordingly, dependent tube drainage was reinstituted, and, after a prolonged period of drainage and irrigation with saline solution, the empyema cavity was reduced to 5 cc., the tube was removed, and the patient was discharged on Oct. 3, 1956. During the course of treatment, the patient had a total of 30 thoracenteses done and cultures made. Only two of these showed infection with Staph. pyogenes var. aureus, coagulase positive, which was sensitive to chloramphenicol and resistant to penicillin, streptomycin, oxytetracycline, and tetracycline. This illustrates one of the adverse effects of giving antibiotics before establishing the diagnosis.

Comment

While most frequently staphylococcic empyema is secondary to a primary bacterial or virus pneumonia, it may be secondary to an entirely extrathoracic infection. The most common method for the development of an empyema is one of the following ways: by lymphatic bacterial drainage into a sterile pleural effusion, by direct extension from the lung itself, by rupture of a subpleural abscess, by septic embolization, and, lastly, by external traumatic or iatrogenic contamination.

All are illustrated in the cases reported here. The mechanism usually varies with the age and primary illness of the patient. In the infant, direct pleural extension from the rupture of a small subpleural abscess during the course of a staphylococcic pneumonia is the most common mechanism. In adults, staphylococcic pneumonia is less common, and, hence, most cases of staphylococcic empyema result from the invasion of the pleural effusion associated with a primary bacterial or virus pneumonia. In the older or chronically ill patient, septic embolization from an extrathoracic source, such as the urinary tract, is a common cause, while in the acutely ill debilitated person, such as is seen with severe burn cases, hematogenous dissemination may occur.

Although the mortality due to staphylococcic empyema has been greatly reduced from its previous high of 50 to 70% in infants and children,[18] the morbidity is still significant. This is due to two factors: delayed diagnosis and inadequate treatment. The diagnosis is frequently difficult. Most adult patients present themselves because of a fever of undetermined etiology after one of the above-mentioned processes. Serial or multiple-view roentgenographic examination may reveal pleural fluid. This most often presents itself in the costophrenic sulcus but may be loculated in the anterior or posterior paramediastinal region and easily obscured on x-ray. In the very young, a characteristic acute bleb formation associated with pneumonia, pleural effusion, and/or pyopneumothorax is quite pathognomonic of staphylococcic infection. This bleb formation was noted in two of the above cases and in 25% of the 41 cases of staphylococcic pneumonia and empyema in children, as reported by Kanof and coworkers.[18] It is believed to be due to a bronchiolar obstruction with the resultant empysematous bleb formation and is to be differentiated from the usual abscess formation which may also occur. These are frequently so large that they are mistaken for a pneumothorax, and inadvertent puncture of the lung with a resultant tension pneumothorax is one of the dangers of repeated thoracentesis for staphylococcic empyema.

The diagnosis, however, must be confirmed by performing thoracentesis with use of meticulous aseptic technique. If purulent material is encountered, surgical drainage, of course, should be performed. Most patients, however, will have received various antibiotics and, in the early stages, have a cloudy effusion which may or may not be positive on culture. It is at this point that inadequate management usually results, and repeated thoracentesis with local instillation of antibiotics is initiated. If an effusion is obviously clear, is a transudate, and is negative on culture, surgical drainage, of course, should not be done. But if an effusion is milky and in reality represents an early empyema, which can

be demonstrated on smear and/or culture, then surgical drainage should be instituted before a chronic empyema results.

The surgical treatment should begin with adequate localization on x-ray, requiring postero-anterior, lateral, and right and left anterior oblique films. Several thoracenteses may be necessary to adequately localize the empyema. Drainage is then instituted. Two types of drainage may be used, depending on the nature of the pus. If a non-loculated fluid is present in the costophrenic sulcus, underwater intercostal tube drainage is necessary. Open drainage would result in a pneumothorax. The empyema of several weeks' duration with a localized accumulation of pus presents a different problem. Because of the inflammatory reaction, pleural symphysis and thickening is present over the remaining lung and the empyema represents a true pocket. This may be drained without underwater protection because the pleural symphysis will prevent the development of a pneumothorax. The site of drainage will depend on the location of the lesion but will usually be in the 6th intercostal space if the pocket is anterior, the 7th or 8th interspace, if lateral, or the 9th or 10th space if posterior because of the varying level of diaphragmatic attachment. The dome of the diaphragm will hinder adequate drainage at lower levels. The tube should be a large one—of the caliber of a 28 F. catheter—and may be inserted with the patient under local anesthesia. This tube is then connected to underwater drainage and, depending on roentgenographic and clinical findings, should remain in place usually for about one week.

In the empyema of several weeks' duration, a more prolonged period of drainage is necessary. Because of the symphysis, open drainage may be instituted as stated above. The opening, however, should be large enough to admit a tubing 1-in. in diameter and to allow easy irrigation, since in this type of empyema mechanical débridement by frequent irrigations is usually more important than the effect of the antibiotics. Accordingly, a subperiosteal 2-in. resection of one or two ribs overlying the dependent area of the pocket should be performed with the patient under local anesthesia. If a prolonged drainage time is anticipated, the skin may be sutured to the pleural edge, creating an Eloesser flap.

Once drainage has been instituted, the problem of duration of treatment arises. The patient is naturally anxious to have the tube removed or the drain site closed. The physician at this point may fall into the error of too early termination of the drainage, since the amount of drainage may actually be very small in a 24-hour period. If the tube is removed, the skin will rapidly close over and an apparent healing take place, only to be followed by a recurrent empyema. It is essential that, during the course of treatment, frequent volumetric recordings of the empyema space be made and contrast visualization of the shape and extension of the empyema cavity performed. The latter is easily done by injecting iodized oil, aqueous Dionosil (propyl ester of 3, 5 diiodo-4-pyridone-N-acetic acid in water suspension with carboxymethylcellulose added), or any of the usual contrast material into the space and taking multiple x-ray views with the patient in the decubitus and erect positions. The volume of the empyema cavity is determined by simply placing the patient on his uninvolved side and injecting sodium chloride solution into the cavity until it is filled. Caution must be exerted here on those patients suspected of having a bronchopleural fistula, lest the opposite lung be flooded. For this reason, the contrast visualization should be performed first.

The duration of drainage will depend on the volume and shape of the empyema space. A drain should be left in place until the volume of the space is 10 cc. or less. Occasionally, a tortuous or dumbbell-shaped cavity develops, and one portion of it may become sequestered or partially blocked from the line of drainage. Although the total volume may then be not more than 10 to 20 cc., this will usually require a second drainage site for expeditious healing. Most empyema spaces will heal within 8 to 12 weeks, even though the original space was several hundred cubic centimeters in volume. Once a true empyema is present, the earlier the drainage the less pleural thickening will occur and the easier it will be for the lung to reexpand. Persistent large empyema spaces, trapped lung, or recurrences will require a more radical surgical treatment, which is beyond the scope of this paper.

Summary

Staphylococcic empyema is a serious and not uncommon disease. Once a true empyema has developed, repeated thoracenteses and antibiotic therapy are not only inadequate, but dangerous. Surgical drainage of the abscess is mandatory and the only satisfactory treatment.

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NOISE—IS IT A HEALTH PROBLEM?

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The permanent hearing loss produced by extended exposure to certain occupational noises constitutes a serious health problem. The solution to this problem lies in active programs of hearing conservation. Hearing conservation is primarily a medical responsibility. The importance of the physician's recognition of his role in meeting the threat to health cannot be overemphasized.

The physician must acquaint himself with the current knowledge of the relations of hearing loss to noise exposure. Misconceptions about the hazardous effects of noise are widespread. Auditory effects of noise exposure and nonauditory effects are frequently related without justification. For example, the fact that a noise produces annoyance does not, contrary to popular belief, mean that exposure to that noise will necessarily produce a hearing loss. The annoyance caused by noise is a highly individual phenomenon and, as such, is not easily measured or predicted. The fact that a noise produces annoyance does not mean that it is bad for health.

The total amount of hearing loss produced by noise exposure depends on more variables than was thought originally. Before the diagnosis of noise-induced hearing loss can be made the physician must have adequate information about (1) the over-all sound pressure level of the noise, (2) the way the energy in the noise is distributed among the various frequencies present, (3) the typical pattern of daily exposure to the noise, and (4) the years of expected work life in the noise. Answers given by the patient cannot be assumed to be reliable, and the physician must make the necessary effort to obtain the pertinent information from reliable sources.

More than 30 centuries ago, according to the old testament, Joshua the son of Nun led the Israelites over the River Jordan and up to the city of Jericho. Here they made camp, and once each day for six days around the walls of the city Joshua led seven priests blowing trumpets made of rams' horns. On the seventh day they compassed the city seven times, and the seventh time when the priests blew on their trumpets Joshua said to the people "shout" and the people shouted with such a great shout that the walls fell down flat. Thus antiquity provides us with the first recorded example of the nonauditory effects of noise. Three thousand years later noise is still blamed, rightfully or not, for a wide range of human ills, from the production of hearing loss to changes in chromosomes to increased admissions to mental hospitals. Today misconceptions about the hazardous effects of noise are rife. It is the purpose of this paper to expose some of these misconceptions and to outline the factual information that is available to help us realistically assess the effects of noise exposure.

What Is Noise?

An entirely satisfactory working definition of "noise" has been difficult to come by. One lexicographer's definition is "Noise is sound without agreeable musical quality." This description has had wide popular acceptance but has proved to be quite inadequate, partly because of the difficulty of defining agreeable musical quality but mostly because of the fact that this quality may be highly undesirable at times. You may keep your taste for contemporary painting concealed from your neighbor, but your taste in modern music cannot easily be confined by walls. What is music of agreeable musical quality to you in your own home may be just plain noise to your neighbor who is trying to sleep in spite of the excellent performance of your amplifier and loud-speaker system. Definitions of noise based on the physical characteristics of sound have not been satisfactory because the definitive characteristic of noise is not physical but psychological, namely its undesirability. The currently accepted definition is "Noise is any unwanted sound."

What kind of measurements must we make to be able to tell how much noise is present in a given situation? Measurement of noise involves measurement of certain physical characteristics of sound. Sound itself consists of propagated fluctuations in barometric pressure. These variations in atmospheric

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pressure may be either periodic or random and are called "sound pressure." Measurements of sound pressure may be used to indicate amount of noise, but it is important to remember that the amount is not the same as the energy in the noise. Just as temperature depends on but cannot be equated to the heat energy present in a body, so the energy in noise is related to but is not the same as sound pressure. It is generally assumed, sometimes incorrectly, that energy is roughly proportional to the square of the sound pressure.

Most instruments for receiving sound, such as microphones or the ear, respond not to the energy in sound but to the sound pressure. For this reason noise measurement scales are based on sound pressure. The smallest fluctuation of barometric pressure to which the young human ear will respond is about 0.0002 of a pressure unit called the microbar. One microbar of pressure is about 0.000001 of normal atmospheric pressure. It follows that the human ear can respond to pressure changes of the order of 0.00000001% of the pressure with which the atmosphere presses on the body. Further, the range of pressure fluctuations to which the normal ear responds is enormous, extending from 0.0002 microbar to 1,000,000 microbars. Because of the astronomical range of figures involved, direct measurements of sound pressure do not provide a convenient scale for measurement of amount of noise.

The decibel scale of sound pressure level was designed to compress this large range of values into a smaller one. The decibel denotes sound pressure measurements combined in a rather complicated way. To find the number of decibels corresponding to a given sound pressure one goes through a three-step calculation. First, the ratio of the measured sound pressure and a standard reference sound pressure is determined. This ratio will have a numerical value. Say, for example, that it is 1,000; that is, the measured sound pressure is 1,000 times larger than the reference pressure. Second, find the logarithm of the numerical value of the ratio; in this case the logarithm is 3. Third, multiply the logarithm by 20: $3 \times 20 = 60$. This number, 60, is the sound pressure level or SPL (in decibels) of the given sound relative to the reference pressure. The word "level" is extremely important. It indicates comparison between the given sound and a reference sound. It connotes a relative measurement, not an absolute one. Sound level meters are designed to read an average sound pressure level in decibels re a standard pressure of 0.0002 microbar. It is important when expressing sound pressure level to identify the reference pressure. More than one such reference is in common use. Hearing level, for example, is expressed in decibels re average normal hearing, not re 0.0002 microbar. Sound-pressure levels typical of familiar noises are shown in figure 1.

Knowledge of just the sound pressure level of the noise is not sufficient to allow us to assess the effects of that noise on man. We must also know something about the way the sound energy is distributed over the different frequencies or tones in the noise. Noises commonly encountered in industry and in our domestic life consist not of single tones but of combinations of perhaps thousands of different tones sounding at the same time. The ear responds differently to different frequencies, and we must have a means of indicating which frequencies are present in a noise and with what intensity. One method of getting this information is to divide the range of audible tones into a series of bands and to measure the sound pressure level in each band. The separate bands are chosen so that the frequency of the highest tone in the band is just twice the frequency of the lowest tone in that band.

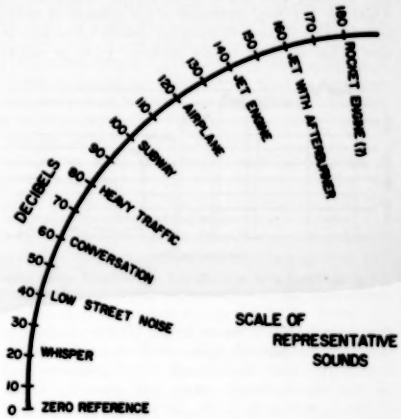

Fig. 1.—Typical decibel sound pressure levels of familiar domestic and occupational noises.

The highest tone is then an octave above the lowest, and the bands are known as octave bands. A rough picture of the distribution of energy throughout a noise may be seen from a display of the sound pressure levels in each of the octave bands. Figure 2 is such a display. Ordered from lower pitch to higher pitch, the bands include the following frequencies: first, 37.5 vibrations or cycles per second (cps) to 75 cps; second, 75 to 150; third, 150 to 300; fourth, 300 to 600; then 600 to 1,200; 1,200 to 2,400; 2,400 to 4,800; and 4,800 to 9,600. In the discussion that follows we shall refer to (1) over-all sound pressure levels, which are average sound pressure levels of the total noise without regard to the frequencies present and (2) octave band sound

pressure levels, which give a rough indication of how the energy in the sound is distributed among the different frequencies.

Effects of Noise Exposure

The known effects of noise exposure are of two types: (1) nonauditory effects, which cause interference with communication by speech or which otherwise influence behavior and (2) auditory effects, which consist of temporary hearing loss and permanent hearing loss.

Nonauditory Effects.—We will consider first the nonauditory effects of noise exposure.

Speech Interference: Perhaps the best understood nonauditory effect is interference with communication by speech. Noises that are not intense enough to cause a hearing loss may interfere seriously with communication by speech. The average of the sound pressure levels in three octave bands, 600 to 1,200 cps, 1,200 to 2,400 cps, and 2,400 to 4,800 cps is a good indicator of the amount of interference that noise will have on speech communication. This average sound pressure level is called

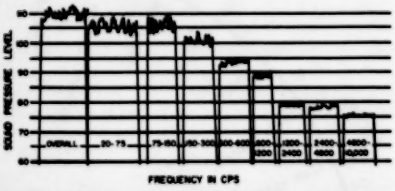

Fig. 2.—Display of over-all and octave band sound pressure levels of noise in multiengine bomber.

the speech interference level. If one wishes to converse in normal tones with someone who is 5 or 6 ft. away, the average sound pressure level in the three bands must not exceed 50 db. If one is willing to shout, the sound pressure level can be as high as 68 or 69 db. If one is willing to converse in a shout at a distance of no more than 6 in., the speech interference level can be as high as 90 db. Note this last number. Noises with this average sound pressure level in the three octave bands may be potentially damaging to hearing. In fact, a rough way of detecting hazardous noise exposure is to determine whether one must shout at close range to communicate by speech.

Annoyance: Perhaps the most talked about nonauditory effect of noise exposure is annoyance. It is a common error to equate the annoyance produced to the potential menace to health that might result from exposure to the noise. There is no necessary connection between annoyance and potential damage or between lack of annoyance and lack of hazard. Actually certain well-deplored pastimes of the human race attest to the fact that the pleasantness of a stimulus is not necessarily an indication of its beneficial effects on health.

The annoyance caused by noise is largely a psychological response. Noises made by neighbors and by their dogs tend to be more annoying than the same noises made by members of our own households. The annoyance caused by aircraft noise is intensified by the fear that the aircraft may crash onto us. It is especially annoying to have to listen to speech that is just too faint to be understood.

How can we measure annoyance? One way is to check complaints. If the noise brought forth a law suit, it was indeed annoying to someone. There are other less drastic but perhaps less realistic methods for rating annoyance. We can conduct opinion polls and ask community members if such and such a noise is annoying, and we can reproduce noises in the laboratory and ask subjects to rate them according to annoyance. None of these methods is really satisfactory. In general, higher intensity, higher frequency (above 1,500 cps), and intermittency tend to increase annoyance, but there are large individual differences in reaction. Annoyance itself is not a health hazard, and the fact that a noise is annoying does not establish it as a damage risk.

Efficiency: A third nonauditory effect of noise exposure is possible loss of efficiency. Efficiency in performing mental and motor tasks under various conditions of noise exposure has been much studied because of its practical importance. A major weakness in the design of experiments, however, has tended to invalidate most of the studies conducted in industry. This weakness is the failure to control changes in the non-noise-related environment. Frequently when the noise environment changes, it is because there has been a move to a new building or a change in process accompanied by changes in work tasks, in temperature, or in lighting. Changes in efficiency are known to be caused by any one of these non-noise changes in environment.

Other difficulties with industrial tests of efficiency are that the numbers of employees participating in the studies have been too small to average out the effects of individual differences or even to allow us to estimate statistically what effect these differences might have on the results. Further, a psychological factor enters here. It has been found that the performance made on first encounter with a test seems to persist even through environmental changes. This means that if an employee did poorly on a test given to him first in noise, he would tend to do poorly on subsequent administrations of the test, even in quiet—and vice versa. The conclusions drawn from the most reliable tests of efficiency in industrial noise are that unfamiliar noise temporarily reduces efficiency but that when an employee becomes accustomed to the noise his efficiency returns to a non-noise performance level.

Physiological Changes: Certain temporary physiological changes also occur in the human body as a direct result of noise exposure. The usual emergency reactions of the body occur in response to sudden sharp sounds such as gunfire. There may be a sharp muscle contraction over the entire body. The breathing rate may increase. Blood pressure rises. The heart rate increases. There is an increase in sweating. It is possible that a frequent recurrence of these changes might impair health. Fortunately, the magnitude of these physiological responses wears off rapidly with repetition of the noise exposure.

Summary: The interference of noise with speech communication under a variety of conditions is well understood and can be predicted from measurements of the sound pressure level in certain octave bands of the noise. The annoyance caused by noise is a highly individual phenomenon and as such is not easily predicted or measured. The fact that a noise produces annoyance does not mean that it is bad for health. Efficiency in the performance of mental and motor tasks in industrial settings is only temporarily affected by exposure to unfamiliar or intermittent noises. Physiological changes resulting from noise exposure lessen with repetition of the exposure. At typical industrial noise levels it appears that no unhealthy physiological reaction results even from prolonged exposures.

Auditory Effects.—The auditory effects of noise exposure are of two types, temporary and permanent. The existence of temporary hearing loss, often called temporary auditory threshold shift, or TTS, and of permanent hearing loss can be demonstrated easily. The auditory effects of noise exposure constitute a serious health problem. Twenty-five per cent of preemployment audiograms show significant hearing losses. Factory workers show nearly twice the hearing loss that office workers show when ages are the same.

Temporary Hearing Loss: Temporary noise-induced hearing loss is a loss that results from a specific exposure to noise and that disappears in some arbitrarily chosen length of time. Strictly speaking the term "temporary hearing loss" might be interpreted to mean any hearing loss from which the ear recovers, no matter how long a recovery is required. The term, however, has become somewhat restricted by usage to mean either a temporary disability as defined by law or a hearing loss that results from one day's exposure to noise and from which the ear has recovered usually by the next morning. The latter definition describes the temporary hearing loss found in many industrial employees at the end of a working day. Studies of temporary auditory threshold shift have made us aware of several important facts concerning both temporary loss and permanent loss.

In brief, some of these important facts are as follows: 1. The temporary elevations of auditory threshold that result from various noise exposures may range from no change to increases of 35 db. The shift is different for different persons under the same conditions of noise exposure. Also, temporary shifts produced by typical industrial noise exposure are larger at the higher frequencies in the audible spectrum. 2. Most of the temporary loss produced by typical noise exposures occurs in the frequency region between 4,000 and 6,000 cps. 3. Most of the temporary loss produced by typical industrial noise exposures occurs during the first one or two hours of exposure. 4. The amount of temporary loss and its frequency location vary with the amount and frequency location of any permanent loss present; that is, the more permanent the loss at any frequency, the less the temporary shift at that frequency. 5. Temporary threshold shift is a fairly stable quantity. For a given noise exposure the TTS is about the same for a person from day to day. 6. For any given noise exposure, the TTS varies from person to person roughly according to a normal statistical distribution. That is, few persons have very large or very small shifts. The loss in most persons clusters around an average midway between largest and smallest shift.

It is our hope that further intensive studies of temporary hearing loss will furnish valuable information about permanent hearing loss. On the basis of the preliminary studies we assume that (1) if the noise does not produce a temporary loss it probably will not produce a permanent loss, (2) from the amount of temporary loss produced by one workday's exposure we will be able to predict the amount of permanent hearing loss to be expected after years of exposure to that noise, and (3) the shape of the audiogram showing the temporary hearing loss will resemble the shape of the audiogram recording permanent hearing loss produced after years of exposure. These assumptions have yet to be validated by long-term studies of permanent hearing loss.

From a practical standpoint the temporary threshold shift produced by daily exposure to noise is important in areas other than research. For example, temporary threshold shift is included in the hearing losses recorded by industrial audiometry. An audiogram made immediately at the end of a workday of noise will include temporary loss and will therefore not be a true indication of the amount of permanent hearing loss present. Industry requires a true measure of permanent hearing loss, but it is quite impractical for all industrial audiograms to be made after a quiet period sufficiently long to eliminate temporary loss. We expect that highly controlled studies of temporary threshold shift will result in a numerical method of correcting industrial audiograms for contaminating TTS.

Laboratory studies of TTS have demonstrated that continuous exposure and interrupted exposure produce different effects in the ear. If, for example, a noise is on for half the exposure time, that is, if it follows a pattern of one minute on one minute off, the amount of temporary loss is just half that which is produced when the same noise is on continuously. If a similar effect obtains for permanent hearing loss and if employees are allowed relatively quiet periods at intervals throughout the day, then long-term changes in hearing will be less than changes produced by continuous exposure. The ear apparently has some mechanism for recovery during even short rest periods, which seems to make it less vulnerable to loss.

Permanent Hearing Loss: Long-continued exposure to intense noise can produce permanent hearing loss, but the process of production is not well understood. The end-result, namely, the pathology of permanent noise-induced hearing loss, has been demonstrated in animal ears. Noise exposure produces an inner ear damage which may vary from minor changes in the hair cell endings to complete destruction of the organ of Corti. The mechanism of the production of this pathology is not completely known, but it appears that overstimulation by noise for long periods of time produces a metabolic change in the cell which in turn causes degenerative damage to the cell structure.

The specific causal relations of hearing loss to noise exposure are very complex, and many questions must be answered before definite statements can be made about how much hearing loss will result from a given noise exposure. Investigations so far have produced three particularly important pieces of information about permanent hearing loss. First, serial audiograms of persons exposed to intense noise show a characteristic progression of hearing loss. Early losses appear at frequencies between 3,000 and 6,000 cps. Usually losses appear first at 4,000 cps and then in time spread in both directions until hearing for most of the audible frequencies affected. The extent of the spread depends on the amount of noise exposure sustained. Impairment of hearing is usually not noticed until losses at the speech frequencies, 500, 1,000, and 2,000 cps are 20 db. or more. Substantial losses may occur at frequencies from 3,000 cps to 6,000 cps without producing any subjective awareness of changes in hearing. The production of noise-induced hearing loss is a slow and insidious process, and years of exposure may elapse before any significant noticeable loss of hearing occurs.

A second important piece of information about permanent hearing loss is that we cannot directly equate the deleterious effects of noise exposure and the energy content of the noise. That is, double the energy content in the noise does not produce double the hearing loss. We assume that the larger the total energy content of the noise the smaller the time of exposure required to produce a hearing loss, but the exact relation between time and energy is not known.

A third piece of information is that the total amount of hearing loss produced by noise exposure depends on many more variables than was thought originally. Hearing loss varies with the type of exposure and its degree of intermittency, the individual exposed, the total duration of the exposure, and the degree of consistency of use of ear protection.

Noise Exposure and Permanent Hearing Loss: Throughout the discussion we have referred to the hearing loss produced by noise exposure, not by noise. The concept of exposure, of the need for time of development of hearing loss, is important to the physician. Brief exposures to most industrial noises will produce no illness or damage to the ear. Whenever the causal relations of hearing loss to noise are considered, the physician should consider each of the following four factors bearing on noise exposure: (1) the over-all noise level to which the man was exposed, (2) the frequency composition or spectrum of this noise, probably as expressed in octave band sound pressure levels, (3) the duration and time distribution of noise during a typical workday, and (4) the total duration of the noise exposure expected during the work life.

To elucidate the last two factors consider the following example: The physician is often confronted by persons who work in high-level noise areas, perhaps as high as 130 or 140 db. Before drawing any conclusions about the effects of exposure to these noises, the physician must inquire carefully about the length of time spent in the noise. Brief exposures to these noise levels will not produce severe hearing loss nor in most cases even significant hearing loss. On the other hand the physician also encounters persons who work in lower noise levels, perhaps 100 db., and again exposure time is important. The possible effects of extended exposure to these lower levels must not be minimized. In many instances persons who are exposed to the 100-db. noise have much longer total duration of exposure than do the men who work in excessively high noise levels. If the noise level is approximately 100 db. but the exposure has been long, existing hearing loss may be directly related to the noise exposure.

Some industrial noises will produce significant hearing loss only if the exposure continues over 15 or 20 years. Many operations that are associated with these industrial noises, however, are characterized by rapid job turnover. The total duration of exposure for any man's ears may be not more than two or three years. Exposure to the average industrial noise for two or three years usually produces only minor changes in hearing. If the physician does not have this information about exposure, he should ask for it before making a diagnosis.

These statements are based on the result of our experience with continuous noises. We know very little about the auditory effects of impact noises such as blasts, rifle fire, or drop hammer sounds.

Conservation of Hearing

Because prolonged exposure to many industrial noises can produce a permanent handicapping hearing loss, we must depend on conservation as a solution to the health problem created by noise. Through well-organized and properly monitored programs of hearing conservation, noise-induced hearing loss can be either prevented or greatly minimized.

There are certain rules of thumb for assessing the possible need for a hearing conservation program. Whenever persons have (1) difficulty communicating by speech when they are in the noise, (2) tinnitus after working in the noise for several hours, or (3) a temporary loss of hearing severe enough to muffle speech or other sounds, again after several hours of exposure, the noise exposure is severe enough to warrant serious consideration of a conservation program. A hearing conservation program consists of three parts, as described below.

Analysis of Noise Exposure.—First an analysis of the noise exposure must be made. Four separate items are considered in any such analysis, namely, the over-all level of the noise to which employees are exposed; the frequency composition of the noise; the duration and distribution of exposure during a typical workday; and the total exposure expected during a work life. Knowledge of each of these items is important to the design of an effective program. Two noises may have the same over-all level, for example, and yet their frequency compositions may differ so that one may produce a permanent hearing loss and the other may not. The daily duration and distribution of exposure may affect significantly the severity of the expected loss; intermittent exposure is less hazardous than continuous exposure.

Control of Noise Exposure.—The second part of a hearing conservation program is the control of noise exposure. Some noise exposures may be reduced considerably by changes in the physical environment. The amount of noise produced by the source may sometimes be reduced, for example, by replacing metal gears with fiber gears or by lining conveyor chutes with resilient materials, or by changing the manufacturing process, such as by substituting welding for riveting. In other instances it may be possible to reduce noise levels by preventing the transmission of noise through building structures or even through the air. Mounting heavy machinery on shock-absorbing mounts will tend to prevent vibrations from being transmitted through the floors and walls of the building. Enclosing noisy machines or building heavy barrier walls between machines and employees will tend to prevent airborne sound from reaching the ears of men who work in the machine area but who do not need to be near the machine itself.

Sometimes, when other environmental control procedures are not feasible, it is possible to revise operational procedures in such a way that continuous exposures are converted into intermittent ones. In the event that complete environmental control is too expensive to be practical, control of noise exposure may be achieved through the use of personal protective devices or through a combination of environmental control and personal protection.

Measurement of Hearing.—Perhaps the most important part of a hearing conservation program is the third item in the list of three, namely, measurement of hearing. A hearing conservation program should provide both for preplacement hearing tests and for routine periodic follow-up or re-check tests. Preplacement tests provide reference or base-line audiograms from which subsequent changes in hearing may be determined. To provide an adequate base line these preplacement tests must be threshold tests. Air conduction threshold tests are sufficient. Thresholds are usually measured at six frequencies: 500, 1,000, 2,000, 3,000, 4,000, and 6,000 cps.

Threshold measurements at 3,000, 4,000, and 6,000 cps, sometimes called the monitoring frequencies, give a good indication of the status of hearing in the most sensitive region of the ear. Measurements at 500, 1,000, and 2,000 cps give an indication of the status of hearing in the all-important speech region. In the absence of valid speech tests to determine the handicap produced by hearing loss, the average of the hearing level at the three speech frequencies, 500, 1,000, and 2,000 cps, is used to estimate the hearing loss for everyday speech. Handicap begins at levels above 15 db. and is total at about 80 or 82 db.

Preplacement and follow-up tests together help to identify persons who may be highly susceptible to noise-induced hearing loss. A series of follow-up tests will tell whether the conservation program is effective. Because follow-up tests are made not to establish a base line but rather to detect changes in hearing status, the limitations placed on them are not as severe as the limitations placed on preplacement tests, and follow-up tests of hearing may be screening tests. In some situations they may be single frequency screening tests. A rather extensive survey of existing records of hearing loss in many different groups of persons showed conclusively that in more than 98% of the cases reviewed hearing losses at 4,000 cps were as large as or larger than losses at any lower frequency. This result held true for losses of 50 db. or less. The implication is that the threshold of hearing at 4,000 cps may be considered an upper limit for any threshold shift that may have occurred at lower frequencies. A gross check on changes of hearing can thus be made

from measurements of the 4,000 cps threshold. Other details of the single frequency or limited frequency screening tests will be found in an article by one of us and House.[1]

Medical Responsibilities.—Ultimately the responsibility for conservation of hearing rests largely with the physician, as emphasized in the following statement[2]:

> The conservation of any human function is primarily a medical responsibility. Hearing conservation is no exception. Prevention, diagnosis and treatment of hearing loss; validation and approval of audiometric records; and the final assessment of measurements of hearing are medical responsibilities. Any hearing conservation program without medical supervision must be considered inadequate.
>
> Direct medical supervision of a hearing conservation program is highly desirable. Here a physician is responsible for the organization and administration of the testing program as well as for checking and evaluating audiometric records. The physician himself does not perform all the operations necessary to the conduct of the program: he delegates responsibility for many of the technical activities to members of his staff, setting up standards or limits within which they can operate semi-autonomously. Whenever medical records show that control of noise exposures may be inadequate, the physician in charge so reports. The responsibility for making necessary noise measurements and for effecting further environmental noise exposure control then devolves on the industrial hygienist, members of the engineering or safety departments or other persons assigned to the task. Although the actual operations of measurement and protection are performed by both medical and non-medical personnel, the physician ultimately is responsible for the health of the employee.

Conclusions

The nonauditory effects produced by typical industrial noise exposures—speech interference, annoyance, changes in efficiency, and physiological changes—do not constitute a health hazard. Whether the nonauditory effects of the extremely high noise levels generated by jet engines and rocket engines will constitute such a hazard remains to be seen.

The auditory effects of noise exposure are a serious threat to health of a large segment of the industrial population. Permanent, handicapping hearing loss can be produced by extended exposure to many industrial noises. We do not yet know enough about the relations of hearing loss to noise exposure to set a safe level of noise exposure. We can say, however, that whenever employees are exposed to continuous noise for at least five or six hours a day, five days a week, 50 weeks a year, for several years; then if the sound pressure levels in any of the three octave bands 300-600 cps, 600-1,200 cps, or 1,200-2,400 cps exceed 85 db., a program of hearing conservation is called for. This hearing conservation level of 85 db. in any of the three specified octave bands does not apply to impact noises. There is not enough information about the effects of impact exposure to allow us to set such a hearing conservation level.

Hearing conservation is primarily a medical responsibility. In our rapidly expanding mechanized civilization noise threatens to become a major health problem. The members of our society look to the medical profession for protection from this threat. The importance of the physician's recognition of his role in meeting the threat cannot be overemphasized.

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ANTIBIOTICS FOR CHILDREN.—The indication is clear that hospital boards may themselves decide to restrict the use of one or more potent antistaphylococcus agents in an effort to retain an "ace in the hole" if a difficult therapeutic problem should arise. Chloramphenicol, novobiocin, and ristocetin might well be restricted voluntarily in order to reserve them for situations of absolute need. A rational approach for the selection of the proper antimicrobial agent in the treatment of children suffering from bacterial disease requires some basic information and a considerable degree of sales resistance to undue or premature advertising claims. It is suggested that the pediatrician formulate a tentative specific etiologic diagnosis when faced with an illness—usually on the basis of clinical impression—but occasionally by employing the help of bacteriologic study prior to the administration of the antibiotic drug and to give such a drug only when indicated. A good rule in therapy appears to be to give a large enough amount of the drug to which the etiologic microorganism is susceptible, by the proper route and as early as possible in infection, and to continue such treatment for an adequate time to ensure eradication of such infection.—C. H. Kempe, M. D., Pediatric Use of Antibacterial Agents, *The Journal of Pediatrics*, July, 1958.

PROLONGED INTERMITTENT STEROID THERAPY FOR NEPHROSIS IN CHILDREN AND ADULTS

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Aqueous ACTH, to induce diuresis, was given for at least 12 but preferably for 21 days, unless marked side-effects necessitated earlier cessation of therapy, to patients with nephrosis and clinical and laboratory findings consisting of massive edema, marked proteinuria (3+ to 4+), hypoproteinemia, hyperlipemia, and, in most instances, a lowering of the serum complement activity. Prolonged intermittent therapy with cortisone, given orally, was begun five days after the onset of diuresis but only when diuresis led to complete freedom from edema. After one year, therapy was gradually terminated by prolonging the intervals between maintenance courses rather than by decreasing the daily dosage. Prolonged intermittent steroid therapy not only resulted in an improved prognosis but also permitted the patients to live a more gainful and happy life. The growth and development of these children has remained within normal limits during and after prolonged intermittent maintenance therapy. Continuous steroid therapy, in contrast, has resulted in marked developmental disturbances.

It is generally accepted [1] that ACTH and cortisone and its derivatives produce remissions of nephrosis in a high percentage of patients. Investigators employing different dosage schedules have observed remissions of varying durations. The purpose of this report is to present the response of a group of patients with nephrosis treated with one specific regimen of intermittent steroid therapy over a prolonged period of time, as originally suggested by one of us.[2]

Selection of Cases

The patients presented in this study had clinical and laboratory findings consisting of massive edema, marked proteinuria (3+ to 4+), hypoproteinemia, hyperlipemia, and, in most instances, a lowering of the serum complement activity. The series includes all of the cases encountered, without exception, of both the so-called pure or lipoid nephrosis and the nephrotic stage of glomerulonephritis (the latter is characterized by elevated blood pressure, increased retention of urea, and a persistent increase of red blood cells in the urine in addition to the nephrotic features). Other diseases which may also be characterized by edema, hypoproteinemia, proteinuria, and hyperlipemia, such as intercapillary glomerulosclerosis (Wilson-Kimmelstiel syndrome), renal amyloidosis, and renal vein thrombosis, were excluded.

Our last report [3] comprised a study of 24 patients. At present, 46 patients (35 children and 11 adults) have been observed for a period of 21 to 84 months, with an average of 40.8 months (fig. 1). The duration of their disease, however, was longer (21 to 159 months) because a number of patients came under observation long after the onset of initial symptoms. All patients have been treated with the same therapeutic regimen.

Therapeutic Regimen

Aqueous ACTH, to induce diuresis, was given for at least 12 but preferably for 21 days unless marked side-effects necessitated earlier cessation of therapy. The following dosage schedule was used: (1) 25 units, intramuscularly, every six hours, for children weighing less than 40 lb. (18 kg.); (2) 40 units, intramuscularly, every six hours, for children weighing from 40 to 75 lb. (18 to 34 kg.); and (3) 50 units, intramuscularly, every six hours, for patients weighing more than 75 lb.

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If the first course of therapy with ACTH did not induce diuresis, a second course with the next larger daily dosage for a longer period was administered after an interval of several days. Patients in whom diuresis was not induced by repeated courses of ACTH, cortisone, or prednisone (the two latter drugs were used only occasionally to study their effectiveness) were treated in the following manner: 30 units of ACTH in 800 ml. of 5% glucose in water was given intravenously during a period of approximately eight hours each day for 10 to 14 successive days.

Therapy with cortisone, given orally, was begun five days after the onset of diuresis, but only when diuresis led to complete freedom from edema. The dosage was 300 mg. (for children weighing less than 40 lb.) to 400 mg. (for children weighing more than 40 lb.), given for three successive days of each week. All patients were treated for one year regardless of prior return to normal of clinical and laboratory criteria, since these were found not to be

reliable for prognosticating the appearance of recurrences. After one year, therapy was gradually terminated by prolonging the intervals between

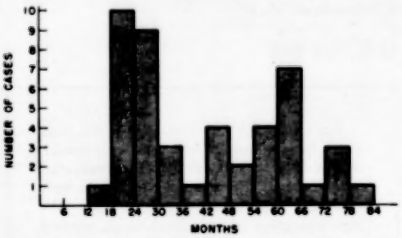

Fig. 1.—Duration of observation of 46 patients with nephrosis (45 living, 1 dead) who were treated with prolonged intermittent steroid therapy.

maintenance courses rather than by decreasing the daily dosage. Most recently we have had good results with large doses (36-48 mg.) of triamcinolone (Aristocort) for induction and maintenance.

steroid therapy. (Early in our studies, however, many patients did not receive antibiotics during maintenance therapy.)

Potassium acetate (30% solution), 0.4 Gm. per kilogram of body weight per day, was given to those patients who showed marked sodium retention and weight gain due to steroid administration. The diet was low in salt (less than 1 Gm. per day) but otherwise unrestricted. Fluid intake was not restricted.

Results

A study of the death rate in the group treated with prolonged intermittent steroid therapy as compared with that in the control group was used as a method of evaluating this suggested regimen.

The control group was composed of patients observed between 1946 and 1951 (a period of 65 months) who were given either no steroid therapy or steroid therapy only when edema was noted. Because the treated group had the advantage of antibiotic therapy, only patients observed subsequent to 1946, when antibiotics became generally

Table 1.—*Therapeutic Results in Patients with Nephrosis—Pooled Data from Group with No Steroid Therapy and Steroid Therapy When Edema Was Noted Compared with That from Group on Prolonged Intermittent Steroid Therapy*

Period, Mo.†	Control Group*							Maintenance Group				
	No. at Start	Entered		Died		Withdrew‡	Death Rate, %§	No. at Start	Entered	Died	Withdrew‡	Deaths Expected, No.
0- 5	48 / 112	160		1 / 2	3	9 / 0	9	1.9		24	0	0	0.46
6-11	38 / 110	148	0 / 14	4 / 7	9	4 / 26	30	6.4	24	3	0	3	1.54
12-17	30 / 98	128	0 / 4	4 / 6	10	2 / 10	12	8.4	24	6	0	5	2.65
18-23	24 / 81	105	0 / 2	0 / 6	6	3 / 9	12	6.0	25	3	0	4	1.47
24-29	21 / 68	89	0 / 2	2 / 6	8	1 / 7	8	9.3	24	1	0	3	2.19
30-35	18 / 57	75	0 / 2	0 / 6	9	3 / 5	8	12.6	23	3	0	1	3.02
36-41	15 / 48	63	0 / 1	1 / 2	3	1 / 6	7	5.0	25	1	0	5	1.13
42-47	13 / 41	54	0 / 0	0 / 1	1	1 / 4	5	1.9	21	0	0	3	0.37
48-53	12 / 36	48	0 / 0	0 / 1	1	3 / 2	5	2.2	18	0	0	5	0.34
54-59	9 / 33	42	0 / 0	0 / 0	0	0 / 7	7	0.0	13	0	1	4	0.00
60-65	9 / 26	35	0 / 0	0 / 1	1	2 / 5	7	3.2	8	1 / 41	0 / 1	2	0.24 / 12.81

* Lower figures from Riley.[4]
† The consecutive six-month periods from the 66th to 149th month included, for the maintenance group, the following data: total number of patients at start of periods, 42; total entered, 5; died, none; total withdrew, 12.
‡ Patients transferred to another type of treatment, e.g., no therapy to maintenance therapy, or those who failed to return to clinic.
§ Number who died ÷ number at start of period + ½ number entering during interval − ½ number withdrawing during interval.

The following antibiotics were given: (1) procaine penicillin G in aqueous suspension, 300,000 units, intramuscularly, twice a day until diuresis was induced, followed by (2) penicillin given orally, 200,000 units, once a day for the duration of

available for the treatment of intercurrent infections, were used as controls. The date 1951 marks the end of the control period because at this time some form of maintenance steroid therapy was used for the treatment of almost all patients with

nephrosis. In the control group were included, with his permission, a number of patients of Dr. C. Riley,[4] to enlarge the total of the control cases.

Table 1 demonstrates, by means of the life table statistical method,[4] the death rate of the control group for each six-month interval that the disease was present during the 65-month period (1946-1951). For example, 1.9% of the patients observed died during the first six months of their illness, and 6.4% died during the second six-month period. The highest incidence of death (12.6%) occurred between two and one-half to three years after the onset of symptoms. The death rate of the control group, for each six-month period, applied to the number of patients observed in the treated group, with disease for the same duration, shows the expected number of deaths during a 65-month period to be 12.8. Actually, only one patient in the treated group died. (One other patient, who died before diuresis could be induced, had had several attempts to induce diuresis with small doses of steroids for 12 months in other institutions and died from an intervening infection.) The probability that this diminished death rate in the treated group was due only to chance is less than one in a thousand (chi square=15.09). Furthermore, observation of the treated group has been extended beyond the 65-month period (for some patients as long as 149 months), and no additional deaths have occurred. Table 1 and figure 2 demonstrate that the actual number of deaths in the treated group was less than was anticipated from applying the death rate of the control group to the number of patients in the treated group. It is less in spite of the assumption that no additional deaths would occur in the control group during a period of observation extended to equal that of the treated group.

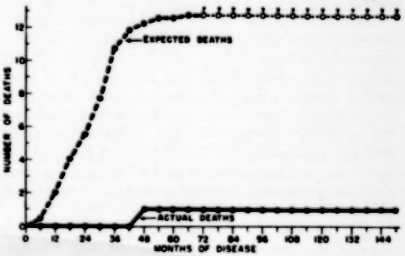

Fig. 2.—Deaths in 46 patients given prolonged intermittent steroid therapy compared to deaths expected on basis of mortality of control group (circles with question marks indicate data not based on actual experience).

TABLE 2.—*Therapeutic Results in Patients with Nephrosis—Data from Group with No Steroid Therapy Compared to That from Group on Steroid Therapy When Edema Was Noted*

Period, Mo.	Control Group*						Steroid Group					
	No. at Start		Died		Withdrew	Death Rate, %	No. at Start	Entered	Died	Withdrew	Death Rate, %	Deaths Expected, No.
0- 5	35 / 64	99	0 / 1	1	3 / 0	1.2		60	2	6	3.5	0.68
6-11	32 / 63	95	2 / 2	4	5 / 20	4.9	52	16	5	7	8.8	2.77
12-17	25 / 41	66	2 / 3	5	7 / 5	8.4	56	9	5	5	8.8	4.54
18-23	16 / 33	49	0 / 2	2	2 / 4	4.4	55	3	4	7	7.5	2.51
24-29	14 / 27	41	1 / 2	3	0 / 2	7.5	47	2	5	6	1.1	3.37
30-35	13 / 23	36	0 / 1	1	2 / 2	2.9	38	3	5	5	1.4	1.07
36-41	11 / 20	31	0 / 1	1	1 / 2	3.4	31	1	2	4	7.1	1.00
42-47	9 / 18	27	0 / 1	1	0 / 0	3.7	26	0	0	5	0	0.87
48-53	9 / 17	26	0 / 0	0	2 / 0	0	21	0	1	3	5.0	0.00
54-59	7 / 17	24	0 / 0	0	0 / 3	0	17	0	0	4	0	0.00
60-65	7 / 14	21	0 / 0	0	2 / 2	0	13	1	1	4	8.3	0.00
Totals			18						30			16.81

* Lower figures from Riley.[4] None entered during interval in control group.

The control group of 185 cases may not be statistically sufficient to represent a universal picture of the course of this disease. The limitation in time, however, between the years 1946 and 1951, makes it difficult if not impossible to collect a much larger control group. In addition, the well-known high

mortality rate, often quoted as 35 to 50%, compared to the one death occurring in 46 treated patients makes such statistical evaluation almost unnecessary.

As described above, the control series comprised two groups of patients: (1) those who received no hormone therapy and (2) those who received hormones only when edema was observed. It is interesting to note (table 2) that the latter group had a statistically significant increase in mortality over the untreated group. We are inclined to believe that the reason for this lies in the fact that patients with severer cases were treated with steroids, while those who seemed initially to have a better prognosis were not so treated.

All patients in the treated group ultimately showed diuresis, although a number required several courses of ACTH therapy, as described above. At present, all are free from edema. In four instances, when all other attempts to induce diuresis failed, intravenous therapy with ACTH resulted in complete diuresis.

There was restoration of normal blood chemistry values (protein, blood urea nitrogen, and cholesterol levels) in all but two patients; one was the only patient in the group who died, and the other is an adult with preuremia and a proteinuria value of 3+. Twenty-five patients have no residual proteinuria, and 19 patients have a trace to 1+ of protein in the urine at the time of writing. Persistent proteinuria seems to occur much more frequently in those patients whose treatment began more than six months after the onset of symptoms. Of patients who were started on maintenance therapy after disease existed for less than six months, 20 showed no proteinuria and 5 a trace to 1+ protein in urine. Of those treated when disease had existed for more than six months, 5 showed no proteinuria, 14 a trace to 1+, and one 3+ (uremia also present). One patient in this latter group died.

A second factor that appears to influence residual proteinuria is the presence of distinct nephritic features (persistent hematuria, granular casts, and elevation of blood pressure) at the start of therapy. There were nine such patients included in this study. The patient who died and the patient with preuremia both had these nephritic features. The remaining seven patients fall into the group with a residual proteinuria value of 1+.

Treated patients were hospitalized only until the completion of diuresis and for the first maintenance course. Thereafter, they were treated as outpatients. Untreated patients who did not die during the first year were hospitalized for an average period of 57 days during each year of observation.

Edema recurred within two to three days after such diseases as upper respiratory infections and exanthem. This occurred in the early phases of our studies when we employed maintenance therapy for shorter periods of time. When the patient was treated promptly with a full course of steroid therapy (12-21 days), such recurrences yielded more readily than the initial episode. In two instances after a second injection of gamma globulin, in one case two days after an injection of Salk poliomyelitis vaccine,[8] and in one case three days after a DPT booster injection, recurrence of edema was observed. Whether immunization procedures with resultant antibody reaction may be hazardous in persons in remission from nephrosis should be studied further.

The growth and development of these children has remained within normal limits during and after prolonged intermittent maintenance therapy.[6] Continuous steroid therapy, in contrast, has resulted in marked developmental disturbances.[7] Prolonged intermittent steroid therapy not only resulted in an improved prognosis but also permitted the patients to live a more gainful and happy life.

No serious adverse side-effects have been noted after prolonged intermittent steroid therapy. Some patients developed moderate elevation of blood pressure (20-30 mm. Hg), both systolic and diastolic, during therapy; this returned promptly to normal values after cessation of maintenance therapy. There was frequently a marked increase in appetite.

A number of our treated patients would probably have experienced spontaneous remissions. Our results, however, and those of other investigators using this regimen,[6] suggest that, for the present, it be followed in all patients with nephrosis. Other regimens,[6] particularly those with smaller hormone dosages, did not lead to equally favorable results. Smaller dosages must, therefore, be considered inadequate from the standpoint of therapeutic effectiveness in the treatment of nephrosis.

Summary

The results of a seven-year study on 46 patients (35 children and 11 adults) with nephrosis who were on a specific regimen of intermittent steroid therapy for a prolonged period showed that the mortality of the treated group was reduced from an expected 12.8 deaths to 1. Furthermore, the patients in the treated group have been able to carry on the normal activities of daily living.

Growth and development were not impaired during or after prolonged intermittent steroid therapy. At present, this regimen, with use of high doses, is recommended for all patients with nephrosis.

1 E. 105th St. (29) (Dr. Lange).

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ACUTE CLINICAL EFFECTS OF PENETRATING NUCLEAR RADIATION

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The experience at Hiroshima and Nagasaki can be correlated with clinical information from other sources (reactor accidents, exposures to radioactive fall-out, and experience with patients undergoing radiotherapy) to predict some of the hospitalization needs of a population in the event of a nuclear holocaust. Victims can be classified as to the form of acute radiation syndrome they manifest, whether cerebral, gastrointestinal, or hematopoietic. Deterioration is fastest, the prognosis worst, and hospitalization least helpful in patients with the cerebral form. The hematopoietic form, by contrast, has a latent period of about three weeks between recovery from the prodromal sickness and onset of the leukopenia and hemorrhage; the prognosis is best and hospitalization most likely to be effective. The gastrointestinal form is intermediate as to duration of latent interval, likelihood of recovery, and effectiveness of hospital care. The hematopoietic form of acute radiation sickness is likely to pose the major problem. The height of hospital occupation then should be reached during the fifth and sixth weeks after exposure, and medical authorities will probably have sufficient time to plan the necessary countermeasures.

In crossing the threshold to the age of nuclear power and space conquest, mankind again experiences the eternal tragedy of ambivalence of its finest technical achievements; they may be applied either in peace, to accelerate general progress and prosperity, or in war, to enhance general destruction and misery. Although it is impossible to foresee the entire complexity of medical problems created by a nuclear holocaust, some basic conditions can be anticipated and must be understood by military as well as civilian physicians.

Historical Development

In both Hiroshima and Nagasaki, the atomic bombs were exploded about 2,000 ft. above the center of the city. At the point of detonation a temperature of several million degrees developed and instantaneously vaporized fission products, unsplit fissionable material, and other parts of the weapons. These highly luminous and radioactive gases, forming the "fireball," quickly ascended into the troposphere where they were cooled, condensed, and dispersed. The city area underneath the explosion, therefore, was essentially affected by only three factors—shock wave, heat originating from the sunlike fireball, and the initial gamma and neutron radiation. Destruction by blast and fire predominated to such a degree that types and distribution of casualties corresponded closely to those seen

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after large-scale bombing raids with conventional explosives; ionizing radiation was a minor complicating factor.[1]

If "altitude air burst"—as executed in the case of the Japanese cities—could be conceived of as the prototype for future warfare, some complacency might be justified. It is one problem to shoot a ballistic missile over a distance of many thousand miles, but it is another problem to hit the target within several thousand feet. Grounds for any such complacency, however, were completely destroyed by the explosion of the thermonuclear bomb at Bikini in March, 1954. This "surface burst" drew general attention to a fourth injurious factor—residual nuclear radiation emitted by fall-out material—and dramatically demonstrated by accidental exposure of several hundred persons that fall-out might become the bomb effect of greatest medical concern.[2] In this surface burst the fireball touched ground and immediately vaporized thousands of tons of soil that were transformed into highly radio-

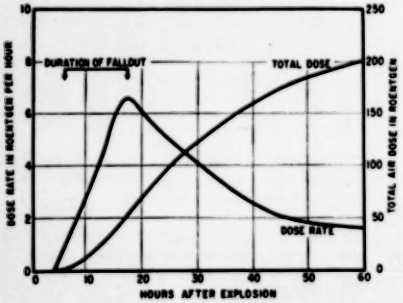

Fig. 1.—Time dependency of dose rate and accumulated air dose at 120 miles downwind from a hypothetical nuclear surface burst. Wind velocity is approximately 30 mph.

active material by the intense neutron flux. As the fireball rose, it caused high winds at the earth's surface and thereby sucked up additional dust and debris. This huge cloud of activated or contaminated material was carried away by the winds at high altitude, and its radioactive particles descended as "fall-out" on the underlying region, where they continuously emitted penetrating ionizing radiation.

As shown in figure 1, the accumulated dose continued to rise with progressing time, although the dose rate, after passage of the cloud, declined because of the decay of radioactivity. Obviously, in the cities and on the air bases engulfed in such a fall-out pattern, military and civilian physicians would face disaster problems and casualties of a type quite different from those in Hiroshima and Nagasaki. Owing to the absence of blast and heat, penetrating ionizing radiation would be the outstanding casualty-causing agent and would produce clinical pictures unfamiliar to most practitioners. The following question would then be of paramount importance:

Is it possible, from the accumulated air dose, to predict type, degree, time course, and incidence of the ensuing disease in a large population and thereby to estimate the medical requirements—personnel, hospital beds, and supplies?

Source of Information

An attempt to answer this question can be based on four sources of information: atomic bomb casualties, nuclear accidents, radiotherapy, and animal experiments. In approximately 10% of the Japanese bomb casualties, initial ionizing radiation was the dominating injurious factor; however, clinical and pathological data cannot safely be related to a corresponding dose, since the intensity pattern of neutron and gamma radiation is largely unknown for the two Japanese cities.[3] About 300 persons have been accidentally exposed to appreciable amounts of nuclear radiation from fall-out or fissionable material; again, the medical findings can only be loosely referred to a specific dose because of the difficulty of estimating radiation intensity after the actual event has passed. Radiotherapy has accumulated a wealth of experience about radiation effects on man. Although only limited portions of the body are exposed as a rule, relatively high doses of whole-body irradiation have been administered occasionally.[4] These observations are particularly important because they represent the only human data with accurately known quality and quantity of radiation. Since radiation effects are of a surprisingly uniform nature throughout the entire mammalian kingdom, large-scale animal experiments are of considerable assistance in understanding the frequently sporadic findings on human beings. In transferring animal observations to man, however, great caution must be exercised, owing to the fact that certain features, especially the speed with which the clinical picture unfolds, are highly characteristic for a given species.

Obviously, each of the four information sources is compromised; the dose may be ill-defined, the subject may be a seriously sick patient, or extrapolation from animal to man may be required. Thus, the answer to the previous question must necessarily be provisional rather than final. Most of the doses quoted should not be considered as firm values but as the best possible estimates with present-day knowledge. Oversimplified and dogmatic presentation of the complex material derives its justification from the physician's need for a guideline in emergency situations. A more detailed report has been given elsewhere.[5]

General Survey and Terminology

Although widely differing in physical nature (neutrons, high-speed beta particles, and gamma or roentgen photons) and origin (atomic bomb, nuclear reactor, cosmos, and therapeutic x-ray sources),

penetrating ionizing radiations are amazingly uniform and comparable in biological effect. Quite in contrast to mechanical and thermal lesions, for instance, overt clinical signs and symptoms do not follow the radiation insult immediately but are delayed for a characteristic span of time. This "latent period" is explained in part by the fact that ionizing radiation temporarily inhibits mitosis in certain sensitive cell systems with high proliferative activity. After irradiation, the organism continues its normal function until the store of mature critical cells is exhausted (e. g., leukocytes), and only then the disturbance becomes overt because of the lack or deficiency of new cell supply. As a rule, since mitotic damage is only transitory, normal function will be resumed if the organism is able to survive the critical period of maximal cell depression. This point is well illustrated by the fact that radiation-induced sterility, epilation, and leukopenia are generally transitory in nature.

The previous concept leads to the following important statements: Severity of radiation injury is decided by dose and individual susceptibility; contrariwise, time course and speed with which the clinical sequelae unfold are essentially determined by the affected cell system. In short, ionizing radiation triggers in the critical tissue a process that then proceeds according to inherent properties of that biological system. Consequently, for a given dose range, the clinical picture will be characterized by that essential organ which has the shortest latent period.

Although the different organs show a wide diversity with respect to radiosensitivity and latent period, for the present problem only three appear to be important: central nervous system, small intestine, and bone marrow, together with the lymphoid tissue (table 1). To trigger acute clinical sequelae in the central nervous system, a dose of several thousand roentgens is required; however, overt disease will then develop within hours. For the small intestine, the threshold dose lies around 500 r, while the latent period is approximately five days. Finally, for the hematopoietic tissue, the corresponding values are about 100 r and three weeks respectively.

Because of these differences, the following responses will occur: At very high doses (suprathreshold for all three critical organs), central nervous system damage will reveal itself within a few hours after exposure and will lead to a characteristic clinical picture—the cerebral form of the acute radiation syndrome—which proceeds while injury to the other two organs is still latent. At middle doses (suprathreshold for small intestine and bone marrow), gastrointestinal injury will start, several days after exposure, a sequence of overt clinical signs and symptoms—the gastrointestinal form of the acute radiation syndrome—which frequently will run its complete course before the still latent bone marrow damage enters the scene. Finally, at lower doses (suprathreshold for bone marrow and lymphoid tissue alone), the hematopoietic form of the acute radiation syndrome will begin to develop about three weeks after exposure.

In addition to the clinical response of the three critical organs, penetrating ionizing radiation also evokes a transitory systemic reaction of an unspecific character which precedes the actual specific disease. This complex of signs and symptoms should be termed "initial reaction" or "prodromal phase" of the acute radiation syndrome.

Prodromal Phase of Acute Radiation Syndrome

In sharp contrast to the uniformity of the specific organ reactions, the systemic response during the prodromal phase varies strongly in different species. In the rabbit and chicken, it is characterized by severe hypotension that leads, not infrequently, to circulatory collapse and even death. In the mouse and rat, it appears as a brief period of listlessness and apathy. In the dog, monkey, and man, it forms a complex closely resembling seasickness or airsickness. As with these diseases, it is easily influenced by individual disposition and psychological factors. In typical cases the sequence is as follows: Within two hours after exposure, loss of appetite, listlessness, and apathy develop rather abruptly and the patient complains about an "upset stomach." Soon, nausea and frank vomiting appear and increase in intensity until they reach their maximal height around eight hours after irradiation. At this time, profuse vomiting not infrequently leads to extreme weakness and even prostration. Thereafter, the distress recedes as fast as it developed. On the second day, nausea and occasional vomiting still persist but the general condition is markedly improved; on the third day, all discomfort has completely subsided. It should be emphasized that the degree of illness depends very much on individual disposition; the same dose that causes incapacitating prostration in one patient may be followed by only

TABLE 1.—*Effects of Penetrating Ionizing Radiation on Man—Schematic Survey*

	Acute Radiation Syndrome, Form		
	Cerebral	Gastrointestinal	Hematopoietic
Determining organ	Central nervous system	Small intestine	Bone marrow
Threshold dose, r	2,000	500	100
Latent period	½-3 hr.	3-5 days	3 wk.
Characteristic signs and symptoms	Lethargy, convulsions, ataxia	Diarrhea, fever, disturbance of electrolyte balance	Leukopenia, purpura, infection
Underlying pathology	Inflammatory reactions in central nervous system, brain edema	Denudation of gastrointestinal mucosa	Atrophy of bone marrow
Time of death (if occurring)	Within 2 days	Within 2 wk.	Within 2 mo.
Cause of death	Respiratory arrest	Circulatory collapse	Hemorrhage, generalized infection
Prognosis	Hopeless	Poor	Good
Source of information	Animal experiments	Animal experiments, bomb casualties, nuclear accidents	Bomb casualties, nuclear accidents, radiotherapy

light episodes of nausea in another.[4] For this reason, severity of the prodromal phase is not necessarily indicative of the seriousness of the ensuing specific organ reaction.

Mild forms of the prodromal phase can be handled by psychological reassurance, with emphasis on the ephemeral character of the distress. More serious forms may require sedatives, such as chlorpromazine hydrochloride, and occasionally the need may arise for parenteral fluid supply to replace the loss caused by profuse vomiting.

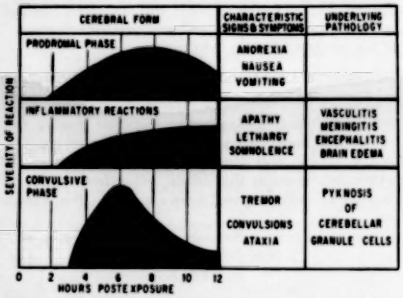

Fig. 2.—Schematic drawing of three components that merge in clinical picture of cerebral form of acute radiation syndrome.

Cerebral Form of Acute Radiation Syndrome

In Hiroshima and Nagasaki the few persons who received doses of several thousand roentgens without suffering from lethal mechanical and thermal injuries were lost during the confusion of the first three days after attack, and only vague reports are available about the cerebral form of the disease in man. Therefore, the clinical picture must be extrapolated from animal experiments. This can be done with a high degree of confidence, since there exists close agreement between species.[6]

The clinical picture can be conceived as the composition of three separate processes (fig. 2). In the manner described before, the prodromal phase starts to develop; but soon a second component is added, the characteristic manifestations of which swiftly progress from listlessness, drowsiness, and languor to severe apathy, prostration, and lethargy. With high probability the morphologic changes responsible for this development are nonbacterial inflammatory infiltrations that appear in small foci widespread throughout the entire central nervous system within one to two hours after exposure. This radiation-induced vasculitis, meningitis, or encephalitis is associated with a disturbance of the blood-brain barrier, leading to brain edema. After doses in excess of 5,000 r, the clinical picture shows a third component, characterized by seizures ranging from generalized muscle tremor to epileptoid convulsions of the grand mal type. This convulsive phase of a few hours' duration is then followed by ataxia, pointing to a vestibulocerebellar disturbance. Convulsions and ataxia, most likely, are consequences of pyknosis developing in the granule cell layer of the cerebellum within two hours after exposure.

Whole-body exposure to doses causing the cerebral form always leads to death. Since heavy sedation prevents seizures in animal experiments, its therapeutic trial seems to be indicated.

Gastrointestinal Form of Acute Radiation Syndrome

Among the Japanese bomb casualties, the gastrointestinal form had terminated its course in the majority of cases before the time when orderly hospital facilities had been restored and clinical records could be kept. And, among persons involved in nuclear accidents, only a few were unfortunate enough to receive a dose capable of causing this form. From the scanty human observations, supplemented by findings made in animal experiments,[7] the typical clinical picture emerges as follows (fig. 3).

On the third day after exposure, when manifestations of the prodromal phase have subsided, the patient's physical and mental condition appears encouraging in outlook. That this favorable state is deceptive and that the latent period is brief are revealed by the sudden onset of the specific disease, starting around the fifth day. Rather abruptly, malaise, anorexia, nausea, retching, and vomiting recur and compromise normal food and fluid uptake. Simultaneously, high fever and persistent diarrhea (rapidly progressing from loose to watery to bloody stools) appear. The abdomen is distended, and peristaltic movements cannot be detected. Rapid deterioration of the patient's general condition soon leads to the clinical picture of severe paralytic ileus. During the second week after exposure, circulation begins to falter, dehydration and hemoconcentration develop, and, finally, the patient becomes comatose and dies in circulatory collapse.

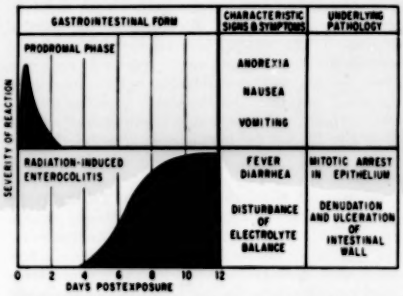

Fig. 3.—Schematic drawing of two components that merge in clinical picture of gastrointestinal form of acute radiation syndrome.

The morphologic substrate behind the clinical picture is located in the small intestine, particularly in the duodenum and jejunum. Normally, the mucosal epithelium that covers the villi is continuously sloughed off into the alimentary tract and is replenished by new cells originating in the generative centers of the crypts. Doses in excess of 500 r inhibit or arrest mitosis in these centers and thereby prevent replacement of desquamated epithelium. As a consequence, denudation of the inner intestinal wall develops, which, in turn, leads to loss of water, electrolytes, and leukocytes. Moreover, absence of epithelium means absence of the barrier against invasion by toxic substances and bacteria. Inflammatory reactions and ulcerative lesions, therefore, are common findings (radiation-induced enterocolitis).

Therapeutic management of the disease, according to Cronkite,[8] has to proceed along the following main lines: Intravenous nutrition, as well as maintenance of water and ionic balance, must be attempted by the supplying of large amounts of electrolytes, plasma, vitamins, and saline-glucose solution. With the onset of fever, expected to occur about five days after exposure, intensive antibiotic treatment should be started. Hemorrhage, anticipated during the second week, will require transfusions of whole blood. Excellent nursing care and aseptic technique are essential.

Hematopoietic Form of Acute Radiation Syndrome

Among the Japanese bomb casualties, the hematopoietic form of the disease has been registered in numerous cases; it was latent during the disastrous conditions of the first weeks after attack, and its overt clinical manifestations appeared at the time when medical care and recording began to return to normal. In addition, clinical histories are available for several hundred persons accidentally exposed to nuclear radiation and for a similar number of radiotherapy patients treated with relatively large doses of x-ray to the whole body. Thus, the disease is well documented for man, and its typical clinical picture is rather firmly established (fig. 4).

On the third day after exposure, when prodromal effects have vanished, the patient becomes asymptomatic and capable of resuming his normal occupation. Although increased fatigability may be present in a few patients, fitness to endure even strenuous physical activity is the rule. This latent period, during which the patient enjoys apparently normal health, may extend to the 19th or 20th day after irradiation, when it ends rather abruptly. As in the acute onset of an infectious disease, the patient experiences chills, malaise, a feverish feeling, headache, fatigue, and shortness of breath on exertion. Within a few days, the general condition deteriorates so markedly as to necessitate hospitalization. Complaints point to a "sore throat," and examination of the oral cavity reveals pharyngitis with swelling, particularly of the gingiva and tonsils. Soon the picture is further aggravated by bleeding from the gums and by ulcerative lesions showing a predilection for the gingiva and tonsils. Concomitant with these processes in the oral cavity, high fever develops, while petechiae and/or ecchymoses appear in the skin. During the fifth and sixth weeks after exposure, this picture of an "agranulocytotic disorder" or an "aplastic anemia" reaches its point of culmination and the patient passes through a critical phase. Thereafter, recovery starts; fever, petechiae, and ecchymoses disappear; and the ulcerative lesions heal. Convalescence begins around the end of the second month after exposure, fitness for resuming normal work is restored about one month later.

The causative substrate behind the clinical picture is mitotic inhibition or arrest occurring in the hematopoietic system. When the store of mature blood cells is exhausted, damage to bone marrow, spleen, and lymphoid tissue reveals itself as pancytopenia. Reflecting the clinical course, white

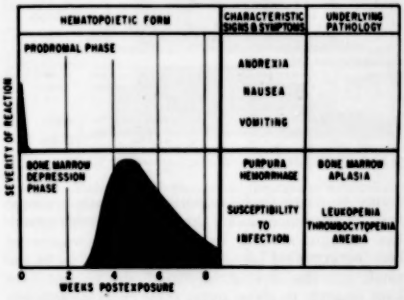

Fig. 4.—Schematic drawing of two components that merge in clinical picture of hematopoietic form of acute radiation syndrome.

blood cell and thrombocyte counts reach their lowest point during the fifth and sixth weeks after exposure and then gradually return toward normal values. The red blood cell count is much slower in falling and recovering.

Since no specific therapy has been developed as yet, complications must be treated as they arise. Purpura and frank hemorrhage require repeated transfusions of fresh whole blood or separated platelets and leukocytes, the frequency and amount of transfusions being determined by the blood cell count. It may be worthwhile to try additional procedures usually applied in other types of agranulocytic disorders. Administration of broad-spectrum antibiotics is necessary to combat localized infections and to prevent their generalization. Under proper management, outcome of the hematopoietic form is predominantly favorable because of the bone marrow's tendency for spontaneous recovery.

Transition Forms

For didactic reasons, the three forms of the acute radiation syndrome have been described as completely independent entities. In reality, these clinical pictures will be separated from each other by broad dose ranges exhibiting a mixture between two adjacent pure forms. Of these transition pictures, that between the gastrointestinal and hematopoietic

TABLE 2.—*Interrelations Between Dose Level and Clinical Picture*

Dose Range, Roentgens	Source of Information	Signs and Symptoms	Clinical Course
15-50	3 volunteers, 4 nuclear reactor accidents, 157 fall-out exposures, numerous radiotherapy patients	No prodromal phase, slight transient lymphopenia, otherwise asymptomatic	Trivial
50-100.....	2 nuclear reactor accidents, 46 fall-out exposures, about 40 radiotherapy patients	Prodromal phase in 5% of cases, slight leukopenia, otherwise asymptomatic	Trivial
100-150.....	1 nuclear reactor accident, about 20 radiotherapy patients	Prodromal phase in 30% of cases, mild leukopenia	Mild, ambulatory
150-200.....	3 nuclear reactor accidents, 64 fall-out exposures, about 40 radiotherapy patients	Prodromal phase in 70% of cases, definite leukopenia	Mild, ambulatory
Hospitalization Threshold			
200-400.....	1 nuclear reactor accident, 22 fall-out exposures (Japanese fishermen)	Fully developed hematopoietic form	Moderate to grave
400-600.....	3 nuclear reactor accidents	2 hematopoietic forms 1 gastrointestinal transition form	Grave Lethal

forms is particularly important for two reasons: first, its incidence among the Japanese bomb casualties is high; second, its therapeutic management may be crowned by success. When damage to the small intestine is relatively mild, the patient lives long enough to show overt signs of bone marrow depression. On the typical gastrointestinal picture is then superimposed severe pancytopenia with purpura and frank hemorrhage appearing during the second week; apparently, their onset is strongly accelerated by heavy losses of leukocytes into the inflamed alimentary tract. This hematopoietic form with gastrointestinal involvement, or gastrointestinal form with hematopoietic complications, frequently has been presented as the "typical radiation disease."

Dose Dependency of the Hematopoietic Form

The hematopoietic form and the corresponding dose range deserve special attention for several reasons: first, fall-out radiation from 15 to 500 r probably will cover the largest land area by far; second, as analyzed by Meyer,[9] many emergency situations may arise in this atomic age which may force military as well as civil defense personnel to accept doses capable of eliciting the disease; and third, as demonstrated by numerous successfully treated cases, this form promises to reward the physicians' efforts. For an exposed population, medical authorities must base estimate of, and preparation for, the ensuing disease on the air dose when it is known (table 2) or on early signs and symptoms when the dose is unknown (table 3).

With the reservation that the quoted values are only guidelines, and with the understanding that the dose actually received by a population will be highly uncertain under emergency conditions, the contents of table 2 can be briefly summarized as follows: Doses below 100 r are of no acute concern to the physician and will require no treatment other than psychological reassurance. In the dose range from 100 to 200 r, about 50% of the population will experience mild degrees of prodromal effects and hematopoietic depression that can be watched and treated on an ambulatory basis. A dose level in the neighborhood of 200 r must be defined as the hospitalization threshold, since beyond this point the full-blown hematopoietic form will appear with all its complications and will show an incidence among the population which will rapidly grow with the dose. This hospitalization threshold is a concept important for medical organizations and logistics. The subthreshold range generally requires nothing but psychological reassurance and precautionary blood cell counts, whereas the suprathreshold range necessitates arrangements for hospital facilities,

TABLE 3.—*Interrelations Between Clinical Picture and Dose Level*

Signs and Symptoms	Dose Indicated Roentgens	Clinical Course Expected
Nausea and vomiting		
Absent	Less than 100	Trivial
Present	More than 100	Surveillance needed
Latent phase		
Less than 2 wk.	More than 400	Gastrointestinal complications
More than 2 wk.	Less than 400	Typical hematopoietic form
Fever		
After 20 days	Less than 400	Typical hematopoietic form
Within 2 wk.	More than 400	Gastrointestinal involvement
Epilation		
Absent	Less than 300	Typical hematopoietic form
Present	More than 300	Possible gastrointestinal involvement
Persistent diarrhea		
Absent	Less than 400	Typical hematopoietic form
Present	More than 400	Gastrointestinal form
Leukopenia		
WBC above 2,500/cu.mm.	...	Mild hematopoietic form
WBC between 2,500 and 1,000/cu.mm.	...	Moderate hematopoietic form
WBC below 1,000/cu.mm.	...	Grave hematopoietic form
Lymphopenia within 48 hr.		
Slight	Less than 50	Trivial
Mild	Less than 100	Trivial
Lymphocytes less than 50% of normal values	More than 100	Surveillance needed

personnel, and supplies. Between 200 and 400 r—perhaps even 500 r—the typical, fully developed hematopoietic form of the disease must be anticipated. Mortality of this form was 50% at the improvised facilities of Hiroshima and Nagasaki; it was 30% at the University of Tokyo; and it is expected to be further reduced at modern hospital establishments. Since the dose range beyond 400 r is poorly documented for man, definite statements

are precluded; however, it is rather certain that, with increasing dose, gastrointestinal involvement will pose a growing problem and will significantly cloud prognosis. Currently available data are insufficient either to support or to contradict the assumption that an acute exposure to 600 r is the highest one compatible with human survival. For further information, attention is drawn to several interesting monographs.[10]

Incidence and Duration of Hospitalization

Susceptibility to ionizing radiation varies widely among individual members of a population exposed to the same dose. It must be emphasized, however, that such variation affects only the severity of the ensuing disease, not its characteristic time course. This statement, important to medical logistics, is underlined by figure 5. The course over time of the white blood cell count is based on large groups of Hiroshima survivors, whereas the doses have been estimated from therapeutic or nuclear radiation data and from animal experiments. Figure 5 clearly demonstrates that, independent of dose, maximal leukopenia occurs around the fifth week after exposure; consequently, severity of disease and incidence of hospitalization will culminate at this critical period. Owing to its characteristic progression, the hematopoietic form will result in a specific pattern in the need for hospitalization (fig. 6). Although based on all human data presently available, the values in figure 6, of course, are still highly conjectural in nature; however, several points essential to military and civil defense planning appear to be rather firmly established. First, existence of a latent period of two to three weeks' duration will allow medical authorities sufficient time to prepare necessary countermeasures; second, the height of hospital occupation will be reached during weeks five and six after exposure; and, third, appreciable numbers of patients can be released after the second month after exposure.

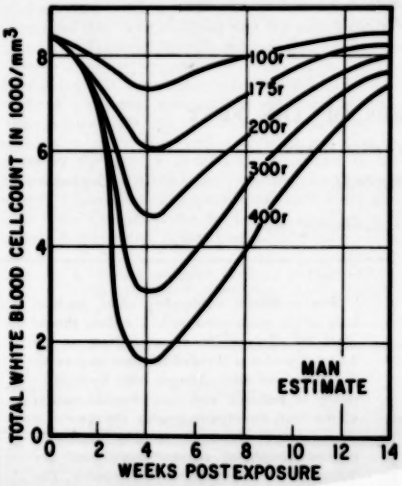

Fig. 5.—Effect of various doses of penetrating ionizing radiation on white blood cell count of man, represented is estimate of mean values for large populations.

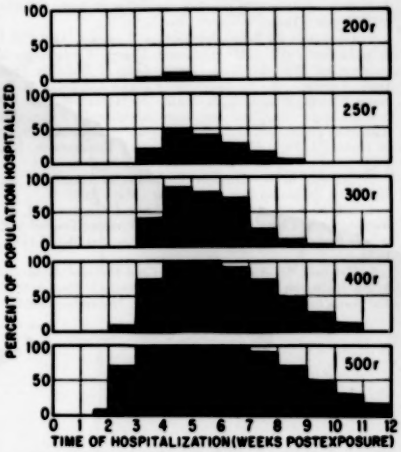

Fig. 6.—Estimate of incidence and duration of hospitalization for populations exposed to various doses of penetrating ionizing radiation.

As in any other severe disease, the acute radiation syndrome may be followed by delayed complications. Induction of leukemia, cataract, or neoplasm has been observed in a relatively small percentage of Hiroshima and Nagasaki survivors. However, the overwhelming majority among both Japanese bomb casualties and persons exposed to nuclear radiation have regained normal health and fitness to pursue their former occupations with full vigor.

Summary

Based on comparative analysis of data derived from radiotherapy patients, persons involved in nuclear accidents, Japanese bomb casualties, and animal experiments, the clinical picture of the acute radiation syndrome is described with its three subdivisions: cerebral, gastrointestinal, and hematopoietic forms. Signs and symptoms are dependent on dose level and individual susceptibility. The hematopoietic form of the disease will probably pose the major problem facing the physician under catastrophic conditions. Some basic rules for medical radiation defense planning are, therefore, de-

rived from the typical time course of the hematopoietic form of the acute radiation syndrome.

Route 3, Box 512 C.

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NEUROTROPHIC ULCERS OF THE FEET

REVIEW OF FORTY-SEVEN CASES

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Neurotrophic affections of the feet masquerade under a multitude of names. Terms frequently used are malum perforans pedis, perforating ulcer of the foot, melanoderma, familial ulceromutilating acropathy, neurovascular dystrophy, and trophopathia pedis myelodysplastica. Neurotrophic ulcer is perhaps the most descriptive term for this group. According to Jelliffe,[1] Nélaton and Vesigne in 1852 were the first to call attention to this condition. Jelliffe reviewed the history of neurotrophic affections of the feet and the early literature, recording 220 articles on this subject prior to 1894.

Early authors recognized the common denominator as damage to sensation, either peripheral or central in origin. Diabetes complicated by peripheral neuropathy is the most frequent cause of

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Any persistent nonhealing ulcer, particularly when associated with a callus, should alert the clinician to neurotrophism as the cause. Opinion is divided to some degree on the bone and joint changes seen by radiography in patients with neurotrophic lesions of the feet. Roentgenographic changes of a degenerative character in any foot with proved peripheral sensory impairment are indicative of neurotrophic arthropathy. The association of bony proliferation that is meaningless or excessive should further alert the clinician. Periosteal thickening, if affecting a site remote from an ulcer, may be significant. Therapeutic measures include simple curettage, removal of the metatarsal head, toe amputation, and major amputation.

such ulcers. Martin [2] in 1954 noted the frequency of neurotrophic disorders of the feet in persons with diabetes. He emphasized the need to recognize this fact and to distinguish these ulcers from those due to infection per se and to occlusive vascular disease.

Myelodysplasia frequently causes neurotrophic ulcers. Jackson [3] discussed errors in the development of the spinal cord and column and expressed the view that cervical and lumbosacral syringomyelia are related entities. Van Epps and Kerr,[4] Lessmann and Poth,[5] and Mulvey and Riely [6] alluded to this close relationship. Whatever the relationship may be, all will agree that both myelodysplasia and syringomyelia are causes of neurotrophic lesions of the feet. Post-traumatic lesions of the cord,[7] tabes dorsalis,[8] and injuries of the sciatic nerve [1] are known causes of neurotrophic ulcers. It is worth noting that tabes is less frequently mentioned in the recent literature.

Opinion is divided to some degree on the bone and joint changes seen by radiography in patients with neurotrophic lesions of the feet. Hodgson and co-workers [9] and Ritvo [10] expressed the belief that changes noted by radiography, attributed to neurotrophism, are in actuality due to infection. In the series of Hodgson and co-workers only 15 of 61 patients had evidence of sensory deficit. Martin [2] contested this view and said that the radiologic appearance of a neurotrophic joint is that of "hypertrophic arthropathy with destruction of the subarticular bone and excessive new bone formation but without periosteal reaction or evidence of bone reabsorption." He has noted such changes without soft-tissue infection or with soft-tissue infection remote to the site of neurotrophic changes in the bones and joints. All of Martin's patients had neuropathy.[11] Changes of a hypertrophic nature without new bone formation can be easily passed over as purely degenerative rather than neurotrophic. Mulvey and Riely [6] have recorded such changes in the first metatarsophalangeal joint, and Martin [2] has recorded them in the midtarsal joint.

Table 1.—*Roentgenographic Findings in Forty-seven Patients with Neurotrophic Ulcers*

Cause of Ulcers	Changes, No.				
	Definite	Mixed	Questionable	None	Total
Diabetes	6	6	6	5	23
Myelodysplasia	2	...	1	5	8
Syringomyelia	1	...	2	3	6
Old sciatic nerve injury	...	...	...	2	2
Old spinal cord injury	...	...	1	3	4
Peripheral neuritis in rheumatoid arthritis	...	...	1	...	1
Neuropathy of herpes zoster	...	...	...	1	1
Tabes dorsalis	...	1	...	...	1
Undetermined	...	...	1	...	1
Total	9	7	12	19	47

Little is found in the literature regarding the treatment of neurotrophic ulcers. Adequate diabetic control and the use of orthopedic appliances to prevent weight bearing on the affected site are important.[2] A two-stage operation, with débridement and packing followed by closure, or with healing by second intention, was advised by Kern.[12] According to Martin [2] local surgical treatment, when combined with antibiotic therapy, can very often save a limb. In his experience ulcers under metatarsal heads can be treated by excision of the metatarsal head in many cases; however, a two-stage operation is mandatory. Kulowski and Perlman [13] said that their results from local surgical measures were disappointing, only 2 of 29 patients receiving lasting benefit; however, these authors reported their results prior to the use of antibiotics and made no mention of using orthopedic appliances to modify weight bearing.

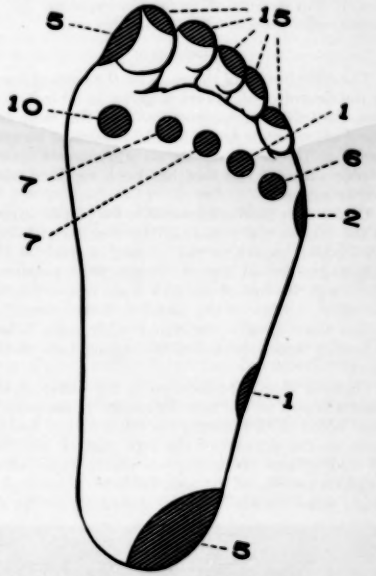

Fig. 1.—Distribution of neurotrophic ulcers in 47 patients. Those on tips of toes were often multiple.

Method of Study

The case records of all patients treated at the Mayo Clinic for neurotrophic ulcers in the period 1946 through 1955 were reviewed; this entailed review of the records of all diabetic patients who had lesions of the feet. Only those diabetics with adequate peripheral circulation, as judged by careful clinical examination, and with evident peripheral neuropathy were included. Follow-up data were obtained in December of 1956 by questionnaire.

Patients with neurotrophic ulcers from other causes were evaluated in a similar manner. Evaluation as to whether the ulcer was neurotrophic was usually a combined effort of the sections of peripheral vascular disease, metabolism, neurology, and orthopedics. In this manner, 47 patients with ulcers due to neurotrophic causes were chosen for study.

Findings

The distribution of the cases on the basis of cause of the neurotrophic ulcers is given in table 1. It is seen that diabetic neuropathy was the most frequent cause, while tabes dorsalis accounted for only one case. To our knowledge no other case of neurotrophic ulcer of the foot has been reported after herpes zoster.

Ulcers were most common over the plantar aspect of the foot in the region of the metatarsal heads. The medial aspect of the plantar surface of the hallux, the lateral aspect of the fifth metatarsal head, and the tips of the toes were frequent areas for ulcers. Ulcers on the surfaces of the metatarsal heads were always associated with thick heavy callosities which preceded the appearance of the ulcer.

Figure 1 shows the location of the ulcers on the plantar aspect of the foot. Fifty-nine plantar ulcers were noted in 46 patients; the other patient had an ulcer on the dorsum of the fore part of the foot. Myelodysplastic neurotrophic ulcers were often noted on the tips of the toes. Diabetic neurotrophic ulcers were confined almost exclusively to the regions of the metatarsal heads and the medial aspect of the plantar surface of the hallux. Ulcers due to the sequelae of lesions of the cord or cauda equina were common on the heel.

Fig. 2.—Neurotrophic ulcers secondary to myelodysplasia. Note pregangrenous condition of toe.

The distribution of the ulcers indicates a mechanical factor. In reviewing these patients' records one is impressed with the architecture of the patients' feet. A broad, splay, or metatarsus latus type of foot with hammer toes, hallux valgus, and prominent metatarsal heads seemed to be the rule.

Characteristically the ulcer was punched out and circular. It was associated with infection and on occasion a pregangrenous appearance. Figure 2 demonstrates this in a patient with myelodysplasia.

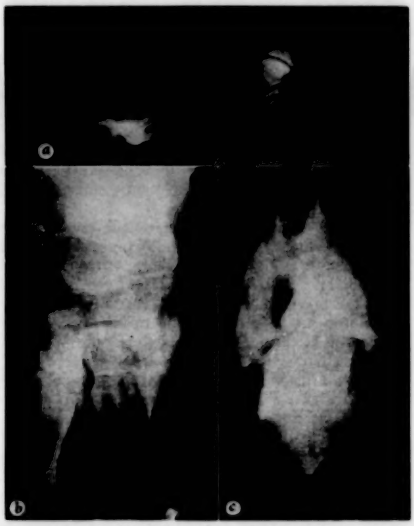

Fig. 3.—Examples of purely neurotrophic changes. *a*, Purely neurotrophic changes at talonavicular joint in 69-year-old diabetic patient. Neurotrophic ulcer of fourth toe, remote from talonavicular joint, had been present only four weeks. *b*, Neurotrophic changes at first tarsometatarsal joint with proliferative changes between bases of first and second metatarsals in 62-year-old patient with myelodysplasia. Neurotrophic ulcers were also present at tips of third and fourth toes remote from site of neurotrophic joint changes. *c*, Typical Charcot ankle in 50-year-old patient with syringomyelia. Neurotrophic ulcer was over second metatarsal head of opposite foot.

The presence of strong pedal pulses and normal venous filling time and the resolution of this pregangrenous appearance with conservative management were in sharp contrast to what is observed in patients affected with occlusive vascular disease. Pinch grafts to the great toe resulted in healing in this patient. Such a lesion in an elderly diabetic person could be mistakenly ascribed to occlusive vascular disease.

Neurological examination is necessary not only to establish a diagnosis but also to map out zones with sensory changes; information on these zones is helpful to the surgeon if amputation is deemed advisable. Sensory alteration which follows dermatome patterns is found in radicular lesions, myelodysplasia, and old injuries of the cord; this is not true in diabetic neuropathy.

All the available roentgenograms of these patients were reviewed. In cases in which roentgenograms were not available for study, the recorded description and opinion of the roentgenologist were accepted; these roentgenograms were nearly all reported as showing no abnormality. In our opinion, changes of a degenerative character in any foot

Fig. 4.—Example of combination of neurotrophic and infectious bony change. Proliferative changes are at first metatarsophalangeal joint. Change in second and third metatarsophalangeal joints is probably secondary to infection. There are changes of neurotrophic nature at first tarsometatarsal joint.

with proved peripheral sensory impairment are indicative of neurotrophic arthropathy. The association of bony proliferation that is meaningless or excessive should further alert the clinician. Periosteal thickening, if affecting a site remote from an ulcer, may be significant. Proliferation and sclerotic changes at the first metatarsophalangeal joint and the midtarsal joints are significant. It is difficult to believe that such changes in the midtarsal or ankle joint could be caused by infection in the fore part of the foot. At the same time "pencilling" of the metatarsals and purely destructive changes in the phalanges and metatarsal heads can be infectious rather than neurotrophic. It would seem logical that these two types of changes could coexist.

Our criteria for assigning a particular bony change are demonstrated in figures 3, 4, and 5. Figure 3 portrays examples of what we call purely neurotrophic changes. Figure 4 demonstrates what we think is a combination of neurotrophic and infectious changes in the joints; we consider this a mixed roentgenographic finding. What we classify as questionable (fig. 5) are probably infectious changes in the bones or joints. The roentgenographic findings in the 47 patients with neurotrophic ulcers are given in table 1 on the basis of the foregoing criteria.

Treatment

Conservative measures are most important in a proper program of therapy. Control of the metabolic problem in diabetes is paramount. Good footwear, with well-placed pads and bars, is essential. It is important that these measures be continued as adjuvants to any surgical procedure. In this series of cases nearly all of these measures had been tried prior to the patient's arrival at the Mayo Clinic.

The surgical procedures used in these 47 patients are given in table 2. The results of these procedures were evaluated 1 to 10 years later. A follow-up period of less than two years was not considered adequate for determining definitive results. The fact that a multitude of surgical procedures had been done on a small number of patients made evaluation difficult. Hence, we shall present here only the impressions that were gained from the follow-up.

For ulcers under metatarsal heads, removal of the toe and the metatarsal head was often successful. In some cases removal of the metatarsal head alone

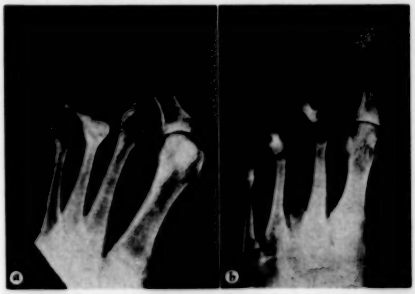

Fig. 5.—Examples of questionable, though probably infectious, changes in bones and joints. *a*, Appearance of foot six years after removal of fifth metatarsal and phalanges of 27-year-old patient with myelodysplasia and five-year history of ulcer over fifth metatarsal head. Third and fourth proximal phalangeal shafts are attenuated. There has been no soft-tissues infection in six-year period since operation. Changes may be secondary to infection or of neurotrophic nature. *b*, Recurrent neurotrophic ulcers in another patient, on plantar surface of fore part of foot for 10 years. Changes in fourth and fifth metatarsal shafts appear to be infectious. Third metatarsal was amputated elsewhere.

was of lasting benefit. This was best performed as a two-stage procedure, and in some cases it was better to allow healing by second intention than by secondary closure. Figure 6 demonstrates an ulcer

so treated. Diabetic neurotrophic ulcers of relatively short duration (6 to 18 months) were most frequently treated in this way.

Below-knee amputation was at times the only answer to a difficult situation in which recurring ulcers, often multiple, had plagued the patient for

TABLE 2.—*Forty-nine Operative Procedures on Forty-seven Patients with Neurotrophic Ulcers*

Operation	Result*	Diabetes	Myelodysplasia	Syringomyelia	Old Cord Injury	Sciatic Nerve Injury	Miscellaneous
Toe amputation	S	7	2	...	...	...	...
	F	2	...	1	...	...	...
	I	1	...	...	...	...	1(undetermined)
Excision of metatarsal head	S	4	...	...	...	...	1(tabes)
Amputation Below knee	S	...	2	1	1	...	...
	I	...	1	...	...	...	...
Syme	S	...	1	...	...	...	...
Transmetatarsal	F	2	...	...	...	1	...
Curettage of ulcer	S	1	...	2	2	...	1(herpes)
	F	2	...	1	...	...	...
	I	2	1	1	...	...	...
Excision and skin graft	S	1	1	...	...	...	1(P.N.†)
	F	...	...	...	1	...	...
Excision and pedicle graft	S	...	...	...	...	1	...
	F	1	...	...	1	...	...
	I	...	...	...	...	1	...
Total		23	8	6	5	3	4

* S = successful; F = failed; I = follow-up inadequate or less than 2 years.
† Peripheral neuritis in rheumatoid arthritis.

years. One Syme amputation was performed successfully in a patient with myelodysplasia. This is significant in that the neurological examination showed that the proposed heel flap had good sensation and points up the value of a neurological investigation. Transmetatarsal amputation was performed only twice, both instances in diabetics, and failed on both occasions. Both of these patients had had recurrent ulcers for 10 years.

Cross-leg pedicle skin grafts failed in three out of four patients. The fourth patient had an excellent early result one year later; the ulcer in this case was associated with an injury to the sciatic nerve.

Simple débridement of the ulcer was successful in some patients. It would seem to be indicated in elderly diabetics with symptoms of short duration, especially if combined with properly fitted shoes and restriction of activities.

Comment

Neurotrophic ulcers have not received adequate attention in recent medical writings. Any persistent, nonhealing ulcer, particularly when associated with a callus, should alert the clinician to neurotrophism as the cause. In the diabetic patient, particularly the elderly one, more thought should be given to prophylactic measures to protect the region of the metatarsal heads. Perhaps routine roentgenographic examination of the feet of the diabetic patient would be advisable.

Once neurotrophic ulcer is an established fact, a variety of therapeutic measures are available. These include simple curettage, removal of the metatarsal head, toe amputation, and major amputation. The duration of symptoms, the age of the patient, and the underlying cause are factors that must be evaluated. In the elderly diabetic with a neurotrophic ulcer of few months' duration, débridement of the ulcer and trimming of the callus, combined with restriction of activity and the wearing of adequately padded shoes, may be sufficient to heal the ulcer and prevent further difficulty.

In patients in the third decade of life with myelodysplasia and prolonged, recurrent neurotrophic ulcers a major amputation may be the only treatment of lasting benefit, but the amputation should be done at the lowest level possible. The chance of involvement of the other foot must be kept in mind.

Fig. 6.—Neurotrophic ulcer allowed to heal by second intention after removal of fourth metatarsal head.

Finally, in diabetic patients lesions of the foot due to occlusive vascular disease constitute an entirely different problem and have been discussed by one of us and Janes [13] elsewhere. Infection, neu-

rotrophic factors, and occlusive vascular disease can and usually do, in some degree, coexist in the diabetic patient. When occlusive vascular disease of a moderate to marked degree is present, the foot must be treated primarily for the occlusive vascular disease. Ill-advised minor surgical procedures may hasten the need for a major amputation.

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RECENT EVALUATION OF THE TREATMENT OF TETANUS

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The plan for managing patients with tetanus has three features: immunization, diagnosis, and sedation. Their effectiveness is shown by experience with 17 patients over a period of 7 years. The mortality was 17%, which is lower than the national average of 40%. As soon as tetanus is suspected, an anesthesiologist is requested to begin sedation by large doses of short-acting barbiturates injected intramuscularly at six-hour intervals. Promethazine hydrochloride is given intramuscularly midway between the barbiturate injections to reduce the anxiety of the patient. A prophylactic tracheotomy is performed under local anesthesia, and a supportive program is then started. The sedation is maintained in order to prevent convulsions with apnea; while it continues, the patient must be turned every two hours to prevent decubitus ulcers and hypostatic pneumonia. After the initial critical period of 7 to 10 days, oral medication generally becomes possible.

Tetanus is an infectious complication of wounds caused by Clostridium tetani and its toxin. It is characterized by local or generalized convulsive spasms of voluntary muscle which may result in periods of respiratory arrest. There is a high mortality—40-50%. Tetanus can occur as a complication of large or small wounds, lacerations, fractures, burns, abrasions, abortions, insect bites, and postnatal separation of the umbilical cord.

The management of tetanus at the Indiana University Medical Center has evolved during the past seven years through treatment of 50 patients, ranging in age from 18 months to 75 years. Management can be accomplished by a coordinated team of anesthesiologist, ear, nose, and throat specialist, internist, and/or pediatrician or by a single physician in a smaller hospital. The success of the treatment depends on early diagnosis. The object is to prevent asphyxia by controlling the muscle spasms and to provide good supportive care.

As soon as tetanus is suspected, an anesthesiologist is requested to begin sedation. Initially, sedation

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is produced by large doses of barbiturates, while a prophylactic tracheotomy is performed with the patient under local anesthesia. A supportive program is then started.

Sedation

Short-acting barbiturates, for example, secobarbital (Seconal) sodium and pentobarbital (Nembutal), are the drugs of choice. Their short action prevents long periods of overdepression while the dosage is being adjusted. The initial dose is 3 to 5 mg. per pound given intramuscularly for children and 100 to 150 mg. given intramuscularly for adults. During the first 24 to 72 hours, this may be given every two, three, or four hours, depending on the judgment of the anesthesiologist as he sees the patient at these intervals. It can be supplemented by the anesthesiologist with intravenously given thiopental (Pentothal) sodium or thiamylal (Surital) sodium if convulsions occur. The intramuscular route is preferred because of the predictable rate of absorption, which is lacking in both the orally and the rectally given medicaments. A continuous intravenous drip is avoided because the patient is more apt to become overdepressed.

The object of the sedation is to prevent convulsions with apnea. The patients will not be flaccid with barbiturates. There will be muscle rigidity and some opisthotonos, but convulsions resulting from external stimuli can be prevented. Some response to stimuli is felt to be beneficial in decreasing the pulmonary complications. As an additional aid in reducing external stimuli and, hence, the total amount of barbiturates given, the patient is placed in a quiet, darkened room, preferably with air conditioning. This is of additional value in maintaining water balance, since the patient with tetanus characteristically has diaphoresis. Some of the usual nursing duties, such as daily baths, must be stopped. However, turning the patient every two hours to help prevent decubitus ulcer and hypostatic pneumonia is essential.

After the initial critical period of 7 to 10 days, it may be necessary to consider oral medication if the patient can swallow adequately. If swallowing is still a problem, then gavage or rectal route is indicated. This is necessitated by the small amount of muscle mass in children compared to the large amount of induration with intramuscularly administered barbiturates.

To meet this problem, promethazine (Phenergan) hydrochloride has been added to the regimen. The adult dose is 25 mg. given intramuscularly every six hours, with the barbiturate given midway between. Four adults have been treated in this manner, and each reported less anxiety about his condition after the promethazine was added. This is important, since the patient with tetanus remains lucid during his periods of wakefulness.

Wound Management

The site of infection, if located, is débrided, and tetanus antitoxin is injected locally. The patient also receives 50,000 to 100,000 units of tetanus antitoxin to neutralize the free toxin. The patient is given a skin test prior to the antitoxin administration, but a routine prophylactic treatment against serum reaction is not done.

Additional care includes hyperventilation by the anesthesiologist and therapy with antibiotics to decrease the incidence of pulmonary complications. Physical therapy is started as soon as possible, usually about two weeks after the patient's admission. This helps to relieve the residual muscle spasm frequently present in the hips, back, and masseter muscles.

Complications

The pulmonary complications have been mentioned. One patient, an 18-month-old boy, required an additional three weeks of hospitalization for skin grafting after a slough from subcutaneous rather than intramuscular injection of barbiturates. As a result of this incident, the nurses record the site of injection so that rotation is assured. Since this procedure was started, one year ago, this complication has not recurred.

Another child developed foot drop from being taped to a sand bag for seven days during intravenous therapy. He subsequently recovered. The veins must be watched carefully for evidence of thrombophlebitis.

A 31-year-old woman died on her second hospital day. She had received psychiatric therapy for an anxiety reaction a few years previously, and her muscle spasm and tight jaw was diagnosed as conversion reaction. Tetanus was not considered until a few hours prior to her death. At this time, the history was obtained of the patient being hit by a piece of brick thrown by a power lawn mower seven days earlier. This case clearly illustrates the need for a high index of suspicion in all cases of muscle spasm and the need for prophylactic immunization of all adults as well as children.

Summary

The management of patients with tetanus at the Indiana University Medical Center has evolved during the past seven years. The curare drugs were used prior to 1955. Since 1955, only the barbiturates and promethazine hydrochloride have been used. There have been 17 patients with tetanus during this time; only three fatalities occurred, and one patient who died had not been seen in the anesthesiology department. This gives a 17% mortality rate, compared to a national average of 40%. All of the patients who died had an incubation period of less than seven days. The three important features of management are immunization, diagnosis, and sedation.

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DIAGNOSIS, TREATMENT, AND POSTOPERATIVE CARE OF BLADDER NECK OBSTRUCTION

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The physician in general practice is important in both the preoperative diagnosis and the postoperative care of the patients with obstruction of the neck of the bladder. The diagnosis is not always easy, for neither the degree of difficulty in urination nor the size of the prostate as judged by rectal examination is a completely reliable criterion for the need of surgery. The author believes therefore that endoscopic examinations should be done oftener than in the past. Experience with 2,160 men who underwent transurethral resection for prostatic hypertrophy during the 12-year period from 1946 to 1957 inclusive showed that the home physician should be prepared for some of the complications that may occur after the patient has left the hospital. These include extravasation of urine, hemorrhage, retention, incontinence, pyuria, stricture of the urethra, and contracture of the vesical neck. Pus, with or without bacteria, usually persists in the urine for several months. The indiscriminate use of antibiotics is to be discouraged. Unless the pyuria is accompanied by other painful or disquieting symptoms, no great effort should be made to eliminate it, since this is impossible until wound healing is complete.

It was suggested that this paper on bladder neck obstruction should be prepared with the interest of the general practitioner in mind and it is our hope that it will be of help to him in attaining a better understanding of the problems of diagnosis, where the diagnosis is obscure, as it not infrequently is, and of the problems connected with the postoperative care of the patient after he has been returned to his home, which often is a considerable distance from the hospital in which his operation was done.

The extent to which the referring or home physician can participate in the postoperative care of these patients depends on his interest, his training, and his equipment. Not every family physician has the equipment in his office for catheterization, bladder lavage, and the passage of sounds, nor does everyone care to take the time necessary for that phase of treatment. Nevertheless, a thorough understanding of the problems that may arise during the postoperative period will help the family physician to contribute greatly to the recovery of the patient.

Diagnosis

Bladder neck obstruction in men is usually due to an enlargement of the prostate or to contracture of the margin of the vesical outlet, and the diagnosis is suggested by the patient's story of having difficulty in passing urine. This difficulty may vary from nothing more than a slight reduction in the size and force of the stream, with a tendency of the stream to be interrupted, to a complete retention of urine requiring immediate catheterization.

The degree of difficulty experienced by the patient cannot be depended on as a criterion of his need for surgical treatment, since occasionally large amounts of residual urine and even renal damage from back pressure will be found in men who have been having only the slightest amount of subjective difficulty. Nor can the size of the prostate as determined by rectal palpation be depended on as a measure of the degree of bladder neck obstruction present, since in many instances the obstruction will be due to an intravesical enlargement of the prostate, not palpable through the rectum, or to a collar of tissue at the vesical outlet.

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Because of these and other considerations, we make endoscopic examinations promptly on men whose symptoms even slightly suggest obstruction, if other findings have not enabled us to evaluate the situation satisfactorily. A 16 F. or an 18 F. panendoscope is used and the examination can be made in the office in 5 to 10 minutes without anesthesia and usually with very little pain or reaction. The information obtained by this procedure permits an evaluation of the degree of obstruction and of any need for surgical intervention.

Treatment

There are several operations for the relief of bladder neck obstruction and, with drugs to control urinary sepsis, better anesthesia, and a better understanding of physiology, each operation is relatively

safe when compared with the experiences of 20 years ago. Some urologists prefer one method and some prefer another but the majority recognize that the transurethral resection is best suited in those cases in which the amount of tissue to be resected is small, and perhaps a majority will, when possible, prefer to use the transurethral method in operating on their extremely aged and especially poor risk patients.

Certain advantages are claimed for each procedure but the principal advantage claimed for the open enucleation operations, such as the retropubic, the suprapubic, and the perineal prostatectomies is that there is less postoperative morbidity from persisting urinary infection because of the more complete removal of the prostate than is sometimes accomplished by the transurethral method. Of course, this depends entirely on how thoroughly the prostate is resected transurethrally, for if it is adequately resected the patient is no more likely to have prolonged difficulty than if one of the other methods had been used. Neither is it to be understood that any of the enucleation operations, done by open operation, will prevent the recurrence of obstruction at a later date, although there is a slightly higher incidence of recurrence of obstruction after transurethral resection.

Occasionally some patient will report that he has been advised to have his prostate removed by open surgical enucleation instead of by transurethral resection so that he would not develop cancer of the prostate later on. This argument is, of course, entirely specious. No matter what method is used any patient may subsequently develop carcinoma of the prostate, since it usually develops in the posterior lobe which is not removed by anything less than a radical prostatectomy.

On the other hand, the transurethral operation is less likely to result in a stormy postoperative course and carries with it a lower operative mortality than do the other methods. This in spite of the fact that it carries an added burden imposed by its use in the extremely aged and poor risk patients. Also it is less likely to be followed by incontinence of urine and is less likely to produce sexual impotence, which is important to some.

As to the restriction of the transurethral resection to the smaller prostates, that, of course, is a matter that has to be decided by each individual surgeon. As the physician's experience in doing transurethral prostatectomies increases, he will be inclined to apply it to larger prostates. Certainly the operation can be long and tedious and requires painstaking care.

Some urologists take the position that a prostate should not be resected transurethrally if it is anticipated that the procedure will require more than an hour, but we cannot agree with the validity of this conclusion. With satisfactory low spinal anesthesia under the supervision of a competent anesthesiologist and with careful attention to hemostasis throughout the operation, it has been our experience that one hour or three hours makes little difference except in the weariness of the operator.

This discussion is based on an experience with 2,529 transurethral prostatectomies done on 2,160 men during the 12 years prior to 1958. All of these were private patients and all were operated on by one of us (E. H. R.), who personally provided most of such postoperative care and treatment as was required.

The patients' ages ranged from under 50 years to 97 years, with 16 being above 90 years of age. Most were in good physical condition generally, but many were severely debilitated from degenerative diseases, having developed urinary retention in conjunction with such things as cerebral vascular accidents and coronary thrombosis. Having been admitted for one condition, they could not be rehabilitated until after being relieved of the associated obstruction and, although constituting an advanced risk group, they had to be operated on in spite of the realization that the hazards of surgery were exceedingly great. If concern for our statistical record had been allowed to be of influence, suprapubic cystostomy instead of transurethral resection might have been used in many of these poor risk patients. It seemed, however, that transurethral resection did not carry much, if any, greater risk than suprapubic cystostomy, so transurethral resection was undertaken.

In this series there were 25 deaths for a percentage of 1.04, and in arriving at this figure multiple resections during the same hospital admission have been counted as one. Six deaths which were counted as operative deaths occurred 26, 35, 38, 42, 60, and 67 days after operation and were included because for one reason or another the patient remained in the hospital far beyond the time he might have been expected to do so. Most of these six were nursing problems when admitted to the hospital and were allowed to remain in the hospital after operation for lack of facilities at home. If a less rigid statistical standard had allowed the elimination of these six cases as operative fatalities, the percentage would have been reduced to slightly less than 0.8%.

Complications and Postoperative Care

A statistical review of this entire group of patients has not been completed, but such a review of a number of consecutive cases is perhaps sufficient to establish a reliable trend.

Urinary Extravasation.—Four patients out of a group of 888, or 0.045%, had perforation of the capsule at the time of operation, with extravasation of the irrigating fluid. All occurred as the resections were being completed and were characterized by lower abdominal pain and rigidity of the abdominal wall. All were recognized promptly and relieved by suprapubic drainage of the prevesical and lateral vesical spaces. All four patients recovered without further incident.

Postoperative Bleeding.—Bleeding may be slight to severe and may occur anytime from immediately after the operation until the time of complete wound healing, with the tendency to bleed being gradually reduced as wound healing takes place. In our experience troublesome bleeding rarely occurs after three weeks but has occurred six weeks after operation.

Most of the time the bleeding will be controlled by the use of an indwelling catheter with irrigations through a semiclosed apparatus making use of a gradual decompression feature. We use a 22 F. self-retaining catheter with 10-cc. balloon and do not pull it down. Neither do we waste much time trying to control severe bleeding with irrigations but prefer to return the patient to the operating room before there has been much loss of blood. Of 888, 15 (1.6%) had to be returned to the operating room for control of postoperative bleeding.

After returning home, many patients will experience the passage of small amounts of blood at the beginning or at the ending of urination. This need cause no concern, but if it is found that clots are being formed and that the patient is having some difficulty in expelling them, prompt intervention is indicated and the patient should be returned to the care of the urologist as quickly as possible. If complete retention has already occurred, catheterization by the home physician may remove enough of the contents of the bladder to make the trip back to the hospital less of an ordeal than it would otherwise be.

Postoperative Retention of Urine.—A number of these patients will be unable to urinate adequately after the catheter has been removed and may continue to have moderate to large amounts of residual urine for days and even weeks after the operation. This is not necessarily due to any inadequacy of the resection, although that possibility should be thought of first and either ruled out or discovered by endoscopic examination before too much time has been wasted. Many times the persisting retention will be due entirely to an atonicity of the bladder, perhaps the result of arteriosclerotic changes in the cord or to long-standing overdistention of the bladder prior to surgery. Most of these patients will gradually improve to the point of complete or almost complete emptying of the bladder, although the weeks required for this to be achieved are among the most discouraging for the urologist as well as for the patient.

The presence of a large diverticulum of the bladder may at times be the only reason why some patient fails to empty his bladder satisfactorily after operation, for even in the presence of a competent detrusor the inelastic walls of the diverticulum will allow large amounts of urine to be retained there. Only surgical removal of the diverticulum will correct this situation.

Incontinence of Urine.—In this group of 888 patients, 3 (0.033%) had incontinence of urine which persisted after wound healing had occurred and inflammation had cleared. Many experienced a transitory small degree of incontinence after the operation, consisting of nothing more than the loss of small amounts of urine on coughing, sneezing, or on suddenly getting up out of bed or out of a chair. Sometimes this loss is the result of the urgent desire to urinate which results when an amount of urine accumulates in the as yet unhealed bladder. When such incontinence is only slight in degree and not the result of persisting inflammation, a routine of exercise for the strengthening of the muscles of the perineum in which the patient is instructed to practice starting and stopping the urinary stream repeatedly will often help to overcome the tendency to leak.

Persisting Infection.—All patients whose prostates have been operated on, no matter what the method, may be expected to have infected urine for a long time. In the majority, if the obstruction has been completely relieved, the infection will gradually clear up, requiring little or no help from the physician. Unless accompanied by symptoms, the mere presence of pus in the urine during this period should cause no concern.

If the patient, however, during the early weeks or months after the operation is found to be having much frequency of urination, with discomfort, marked infection of the urine, and perhaps not an entirely satisfactory stream although he may be emptying his bladder completely as determined by catheterization, the presence of remaining obstruct-

ing tissue has to be suspected and the sooner it is discovered the better it will be for all concerned. The passage of a 14 F. rubber catheter coudé should enable one to discover any stricture of the anterior urethra as well as the presence of any residual urine. The absence of residual urine, however, does not give assurance that there is no impediment to the passage of urine and much can be learned by watching the patient urinate. A large, robust stream starting promptly and continuing without interruption to conclusion is very good evidence of a satisfactory function. If the stream is slow to start, however, is something less than forceful, and tends to be interrupted, it is to be suspected that an obstruction at the neck of the bladder does exist and endoscopy will probably reveal the presence of intraurethral intrusions from the lateral lobes of the prostate, usually at the apex, which will have to be resected before the patient can obtain a satisfactory result.

It is very difficult to have to tell such a patient that he needs further surgery, yet it is better to be in a position to tell him yourself than to have him learn the dismal fact from another urologist.

On the other hand, the patient's difficulties may not be the result of inadequate surgery at all, but may be due to the fact that he has a severe infection by one of the more virulent bacteria and until effective medication is used it may be impossible to give him relief. The difficulty of eliminating such infections is often made more difficult by the presence of severe trabeculation with cellules and small diverticula in the walls of the bladder that tend to retain infected urine.

Since all of these patients should be expected to have pus in the urine, with or without bacteria, for an average of several months, it is not necessary to be concerned about its presence during this period unless accompanied by painful and unduly frequent micturition. Unless such symptoms are present, no great effort should be made to eliminate the pus from the urine, since this cannot be accomplished until after wound healing has been completed.

It has been our practice in the average case, having used chloramphenicol (Chloromycetin) preoperatively and for several days after operation, to keep the patient on therapy with methenamine mandelate (Mandelamine), 0.5 Gm., four times a day for three to four weeks longer and to make use of other drugs only as indicated. The indiscriminate use of antibiotics is to be discouraged and they should be withheld until a definite need is established.

Stricture.—Stricture of the anterior urethra occurred in 9% of 474 of these patients, and most strictures occurred at or just proximal to the external urethral meatus and in spite of the fact that meatotomy was done before introducing the resectoscope when the meatus was at all tight. These strictures usually manifest themselves early in the postoperative period within a matter of three or four weeks and respond to treatment by frequent dilatations with relatively small caliber sounds up to size 18, 20, or 22 F. After a relatively short time, perhaps a month or two, the tendency toward further contraction disappears entirely. After these so-called premeatal strictures have been discovered and dilated, it is important that the dilatation be maintained by the frequent passage of a sound or sounds, preferably every day for a few days, and then after intervals of two or three days to a week, depending on how readily the stricture yields to treatment. The physician at home can be of great help in dealing with this complication, or the patient himself may be able to maintain the dilation with an instrument lent to him for that purpose.

Contracture of the Vesical Neck.—Contracture of the vesical neck occurred in 1.4% of 474 cases. This is an exasperating postoperative complication which occurs much less frequently than does stricture of the anterior urethra, and occurs much later, often not manifesting itself until long after complete recovery from the operation has taken place. It is most likely to occur in those patients who originally had small prostates in association with a considerable degree of fibrosis at the bladder neck. At times the contracture is so severe that on endoscopy it will have the appearance of a diaphragm with a filiform opening in the center. Some contractures are easily dilatable with sounds but usually require frequent dilatations at varying intervals for an indefinite length of time in order to maintain an adequate passage. Further resection is usually followed by further contraction, and in most cases the use of sounds is preferable and will be effective. In an occasional case a Y-V plasty anteriorly at the bladder neck and the removal of a wedge of tissue posteriorly may be required.

Summary

The diagnosis of bladder neck obstruction may be obscure, therefore endoscopic examination should be used more frequently for evaluation of the bladder neck situation. Transurethral resection was performed 2,529 times on 2,160 men during a 12-year period, with an operative mortality of 1.04%. With the elimination of six questionable cases, the operative mortality would have been 0.8%. The care of these patients during the postoperative period places emphasis on the complications that may occur after they have been dismissed to their homes and to the care of their home physicians.

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STUDIES ON THE IN VIVO SURVIVAL OF GLYCEROLIZED AND FROZEN HUMAN RED BLOOD CELLS

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Ninety-four units of blood have been collected, glycerolized, stored in the frozen state at either –80 C or –120 C, deglycerolized, stored at 4 C, and then used clinically. A technique has been developed for maintaining sterility at every step. Even after storage at very low temperatures for periods up to 19 months, the red blood cells appeared therapeutically comparable to cells stored at 4 C up to 21 days in a standard A.C.D. (anticoagulant acid citrate dextrose) solution. The longevity of red blood cells in the circulatory system of the recipient was studied by using chromium 51 for labeling and was found to be independent of the duration of storage. The loss of red blood cells by lysis during the process as a whole seemed to be due entirely to irreversible random damage during collection and handling rather than to storage at low temperature. The sterility of the system made possible an additional post-thawing storage of the red blood cells for up to 11 days at 4 C before use in transfusions. No transfusion reactions of any kind were noted.

In 1949, Polge and co-workers [1] made the chance observation that animal and fowl spermatozoa could withstand freezing at –79 C if previously exposed to a 20% glycerol solution. In connection with this work, Smith noted that erythrocytes which contaminated the needle biopsy specimens were not lysed by the glycerol freezing method. Although Luyet [2] previously had demonstrated the freezing of thin films of blood, this had proved to be mainly of academic interest. The observation of Smith opened a possible practical method for the long-term preservation of erythrocytes. An immediate program of study was stimulated in both England and the United States in an effort to define the conditions for glycerol freezing. Subsequent reports by Sloviter,[3] Brown and Hardin,[4] Mollison and associates,[5] and Lovelock [6] have defined the range of protection by glycerol and elucidated some of the mechanisms wherein this substance and other polyhydric alcohols protect cells against lysis during freezing. The general biological effects of freezing have been reported in detail by Meryman.[7] At least three effects of glycerol appear to play a role: 1. The type of ice crystal which forms in its presence is small, uniform in size, and less disruptive on thawing than the large, irregularly spaced crystals which occur when ordinary crystalloid solutions are frozen. 2. The liquid glycerol phase prevents the high salt concentration which otherwise occurs when water changes its physical state to pure ice. 3. The glycerol becomes so viscid at storage temperature around –80 C that it imposes a mechanical barrier to the slow diffusion of cell substances in the liquid phase. The fact that a diffusion of surface membrane does occur has been advanced by Lovelock as an explanation for the gradual loss of viability which occurs even at the coldest storage temperatures. Essentially no metabolic activity takes place at –80 C. Theoretically, one would expect to achieve permanent preservation at this temperature. Such does not take place, however, and the simple loss of cellular substance may explain this paradox.

The prolonged extension of red blood cell viability by low-temperature techniques could prove revolutionary to standard blood-banking methods. Unfortunately, however, it is necessary to remove or greatly to reduce the intracellular glycerol concentration before the thawed cells can be used. Practical methods for the dialysis of glycerol out of the red blood cell proved cumbersome and have delayed the translation of this important fundamental discovery into a practical means of handling blood. In 1951, Cohn and associates foresaw the need for a "closed-system" technique for glycerol exchange and modified a bowl of the Cohn ADL centrifuge then under development in such a manner as to permit this type of dialysis.[8] The details of this fractionation system are outlined elsewhere.[9]

It is the purpose of the present communication to report survival studies on human red blood cells processed in the Cohn ADL fractionator and stored for variable times in the frozen state after equilibration with glycerol.

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Methods and Materials

All studies were carried out with blood which was processed in a Cohn ADL centrifuge, with use of a bacteria-free system throughout the entire period from initial blood collection to final glycerolization after storage. This method offers the distinct advantages of semiautomation with conservation of technician time, maintenance of low blood temperatures without exposure of personnel to the cold, and closed-system sterility which makes possible the use of standard refrigerator storage and blood bank methods after removal from the frozen state.

Blood Collection, Plasma, and Addition of Glycerol.—Blood was collected from healthy human donors by gravity flow into plastic bags (or bottles) containing A. C. D. solution (National Institutes of Health formula A). Selection of A. C. D. solution as an anticoagulant did not reflect any special property of this solution. Rather, its use was based on the desirability of comparing final survival data with published studies [10] on red blood cell survival with use of original collection into A. C. D. solution and standard 21-day storage at temperatures above freezing. Recent studies [11] have indicated that an isotonic citrate-phosphate-dextrose solution minimizes initial damage during collection of blood which might diminish the loss of red blood cells during processing. The blood was next connected to the red blood cell plasma separation bowl of a Cohn centrifuge.

After separation of the plasma, a series of solutions was introduced which effected a gradual introduction of glycerol solution into the red blood cell concentrate in a gradient from zero to 50% glycerol (w/v) over a 45-minute period of time at 17 C. (Solution 1 contained 20% glycerol [w/v] and solution 2, 50% glycerol [w/v], with sodium lactate, 0.156 M, potassium chloride, 0.004 M, and a sufficient amount of distilled water.) A counterflow method of introducing glycerol inside the revolving bowl made possible the maximum intracellular glycerol concentration, in the minimum period of time, with the least cellular damage from osmotic imbalance. Details of the centrifuge speed, temperature, solutions, and equipment are outlined in a separate communication (see page 404). The only variation in technique in the present report was a change in introduction of glycerol to a two-stage method with a gradient from 20 to 50%. This has the dual advantage of increasing the speed of glycerol equilibration and decreasing the osmotic shock to the cells.

At the end of the glycerolizing period, the cells were poured out into an attached bag which was dielectrically sealed and severed from the centrifuge. A sample was removed for bacterial culture, and the bag was placed in a simple cardboard box to protect the plastic, which becomes brittle at the low temperatures of storage. It is then transferred to the –80 C or –120 C locker. The temperature within the bag fell to –45 C within the first two hours but did not reach the final temperature of –80 C for about seven hours. A report by Polge and Lovelock [12] indicates that the rate of freezing and thawing should be slow between 0 and –40 C but is less critical between –45 and –120 C in the presence of glycerol. No attempt was made in the present study to investigate the parameters of optimal glycerol concentration versus time of storage or survival. Original pilot experiments indicated that some temperature below –45 C and some glycerol concentration in excess of 20% was necessary in order to obtain practical yields of cells possessing greater than 70% survival after processing alone. A glycerol concentration of 50% was found satisfactory and was therefore used throughout the study. Later investigation of concentrations between 20 and 50% may reveal equally beneficial effect of lesser amounts of glycerol, but the primary purpose of this study was the adaptation of the closed-system Cohn centrifuge so as to make available large enough amounts of frozen blood to study adequately the survival characteristics. The only variable introduced into the present experiments was the use of two storage temperatures, –80 and –120 C.

Storage of Cells.—Maintenance of steady temperature was striven for throughout storage. Constant recording devices indicated that no major rise in temperature has occurred during the two years the equipment has been in operation. One locker containing 85 units of blood (maximum capacity, 144 units) was stored at –80 C with no significant mechanical troubles and a maximal range of temperatures between –80 and –84 C.

Another locker containing 100 units, maintained at –120 C, gave mechanical trouble on four occasions after it was first installed. During one such period, when it was partially filled, the internal temperature rose to –60 C over a three-day period before the stored cells were transferred to a separate –80 C box. Some of these units subsequently have shown lower yields of cells and higher concentrations of hemoglobin in the supernatant solution but no major difference in survival after transfusion. A full study of the effect of fluctuations in temperature during storage will be the subject of a separate report. Insertion of thermocouples inside bags of blood placed at three depth levels within the lockers showed that the bottom two-thirds of the locker does not have any temperature variation during ordinary operational opening and closing for removal of stored blood. The top one-third of the box is approximately 20% warmer and fluctuates widely over a 30-degree range; it is not recommended for storage unless provision is made for internal circulation of the air.

Removal of Glycerol.—After storage, individual units of blood were removed at stated time intervals, thawed by immersion in a 37 C to 40 C water bath (average elapsed time, 12 minutes), and deglycerolized in the Cohn fractionator. The technique for removal of glycerol is essentially the reverse of the initial processing. A bag of thawed cells was attached to a sterile cartridge of the machine and forced under normal pressure into the revolving bowl. A series of attached solutions was then fed through the revolving cell suspension, providing for a stepwise decrease in glycerol concentration from 50% to less than 1% (range, 0.32 to 0.9%, corrected for glucose). This was achieved by maintenance of an osmotic gradient of lactate ions outside the cells long enough to permit the glycerol slowly to diffuse out before water can shift intracellularly and cause rupture. The rate of water endosmosis was roughly four times as great as that of glycerol exosmosis. It is for this reason, rather than that of possible glycerol toxicity, that nearly complete glycerol removal is desired. Direct transfusion of thawed glycerolized cells would result in prompt lysis when the erythrocytes were exposed to the 0.15 M ionic strength of blood. Lovelock,[13] Sloviter,[14] and others have suggested the use of concentrated glucose solutions to remove most of the glycerol from the cells and to provide for dilution of the remainder. Such methods possess the side-effects of prohibitive volumes of final administration solution and the need for immediate transfusion after processing due to cellular fragility. Moreover, cells processed by these methods showed a short survival time and high rate of in vivo lysis when studied in this laboratory.

The three wash solutions used for deglycerolization are as follows: (1) sodium lactate, 0.498 M, glycerol, 10% (w/v), potassium chloride, 0.004 M, and a sufficient amount of distilled water; (2) sodium lactate, 0.158 M, potassium chloride, 0.004 M, and a sufficient amount of distilled water; and (3) sodium chloride, 0.15 M. The time required for removal of the glycerol varied between 80 and 120 minutes. The cells were then allowed to flow from the centrifuge bowl into a bag containing 60 cc. of the following resuspension mediums: 400 mg.% of dextrose, 20 mEq. per liter of potassium, and sufficient albumin to give a final concentration of 2 Gm.% after dilution by the red blood cell mass. The pH of the final suspenion was 7.1. The bag of resuspended cells was then sealed, severed from the cartridge, and transferred to a standard 4 C refrigerator for storage until use. Simultaneously, a diverticulum of the bag was removed and cultured at three temperature ranges (4 C, room temperature, and 37 C) in thioglycolate broth and Saboraud's medium. Of 419 cultures done in connection with the present experiments, 416 were negative for bacteria or fungi; in the case of the three positive cultures, known breaks in technique occurred at the time of the original stylet connection between the donor's blood and the machine in two instances, and one bag ruptured during thawing.

The estimated loss of cells during processing was as follows: loss and hemolysis from collection, glycerolization, freezing, and deglycerolization, 10%; intact cells left on walls of containers and plastic bags and tubes, 5%; intact cells sacrificed for bacterial cultures and glycerol assays, 3%; intact cells sacrificed for typing, cross-matching, and serology, 1%; and hemolysis from storage in the frozen state, 0.5%. The technique of the study prohibited quantitative study of the total cell mass at each step of each experiment. However, certain general features were consistently noted: 1. The average decrease of 10% of cells from collection, glycerolization, and freezing represents a relatively fixed loss which is part of the processing itself. In occasional experiments this loss was as little as 2%, but a higher figure generally was noted. 2. The 3% loss through bacteriological sampling and glycerol assay can be eliminated almost completely if one wishes to use this type of processing on a routine, blood-bank basis. 3. The 5% loss on the walls of containers, plastic bags, and tubes also can be reduced if one wishes to take greater time to allow complete drainage after transfer from one bag to another.

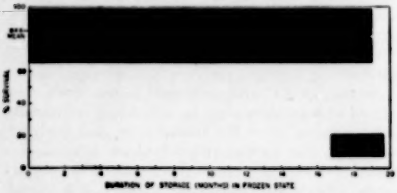
Storage at 4 C.—All cells used in this study were stored at least three days in a standard refrigerator after removal from the frozen state and deglycerolization. The longest postprocessing storage of a blood subsequently used for transfusion was 11 days. This unique advantage of the Cohn closed-system centrifuge processing permits standard shipment to a hospital or medical center where the reconstituted red blood cells are to be used. It also permits an unhurried selection of recipients with proper blood type and cross-matching compatibility. In the present study, no plasma or serum was saved from the original blood donor. Recipient compatibility was therefore based on (1) similar blood group between donor and recipient, (2) compatible "major" cross-match (donor cells and recipient serum), (3) Coomb's cross-match, and (4) resuspension in saline solution and observation for absence of autoagglutination.

An attempt was made to utilize the processed cells within one week after removal from the frozen state. This was because of the gradual accumulation of free hemoglobin in the supernate of the resuspended cells stored at 4 C. The factors responsible for such cell lysis are not understood, but, on the basis of current work, they are believed, in part, to represent inadequate support of the metabolic needs of the cells at refrigerator temperature. Recently, the resuspension medium used for all of the studies reported herein was abandoned in favor of a simple solution consisting of 30 ml. of the original donor's plasma with A. C. D. solu-

tion added plus sufficient glucose to raise the final concentration to 100 mg.%. This has markedly decreased the accumulation of hemoglobin during storage at 4 C. The good survival data obtained on the cells that were still intact at the time of any given transfusion also suggest that the hemolysis at 4 C is not a continuation of damage initiated at the time of processing but that it is a property of the postprocessing storage conditions.

Results

Ninety-four units of blood were collected, glycerolized, stored in the frozen state, deglycerolized, stored at 4 C, and then administered to selected recipients by the methods outlined above. Thirty-three of the units were labeled with chromium 51 prior to final transfusion and studied for subsequent survival in the recipient. All tagging and counting was carried out in the laboratory of one of us (J. G. G.). The untagged units were used directly at the New England Deaconess Hospital as packed red blood cells and were administered for therapeutic use and for observation of recipient effects.



Survival of chromium 51-tagged preserved red blood cells.

Untagged Blood.—No unfavorable reactions of any kind were observed after use of untagged units. This, in itself, seemed surprising, as the original recipients were selected from a hospital population consisting chiefly of patients with fatal blood disorders and far-advanced malignant states wherein pyrogenic blood reactions are anticipated in a significant percentage of cases. Some of the recipients had well-documented febrile responses to ordinary banked blood both prior to and subsequent to the transfusion of frozen cells, without showing pyrogenic reaction to the latter. It is suggested that the absence of fever after transfusion of frozen blood may represent the removal of all plasma components, leukocytes, and platelets, which is an incidental side-effect of the glycerolization process inside the Cohn fractionator.

Recipient red blood cell counts, hematocrit values, and hemoglobin levels, when measured, showed the post-transfusion rise which would be anticipated from comparable amounts of standard banked blood. The maximum number of frozen blood transfusions given to one individual was five. The average volume of the resuspended, packed red blood cells was 350 ml. The administration and therapeutic effectiveness of the frozen blood was in all ways comparable to ordinary banked blood, and no difference in effectiveness was noted between the minimal and maximal storage periods of zero time and 19 months.

Tagged Blood.—All in vivo survival studies utilized chromium 51-labeled red blood cells. Twenty-one units were studied by this method after storage at −80 C for periods between three days and 19 months; seven units were studied after storage at −120 C for periods between five days and 10 months. Studies were also done on an additional five units stored at −20 C prior to availability of the lower-temperature boxes. The techniques for labeling, addition of ascorbate, and counting of samples are reported elsewhere.[15] The volume of labeled cells administered to the recipient was 50, 100, or 350 ml., depending on the specific activity of the radioactive chromium used for tagging and the presence or absence of a therapeutic need for the cells. Samples were removed from a different vein of the recipient 5, 10, and 15 minutes after transfusion, then one and three days after, and then three times per week as long as the patient was available for study. The longest such span was 33 days. Recipient blood volume was estimated on the basis of the first three counts immediately after transfusion. The data for 24 units of blood stored at −80 and −120 C showed a range of immediate survival between 64 and 98%, with a mean of 84.6% (see figure). Two findings are worthy of comment. First, there was no apparent effect from storage time per se. That is, within the period covered by this study, cell survival seemed to be independent of time and reflected merely the effects of processing alone. Red blood cells currently in storage will be studied at future time increments to determine the interval at which loss of cells from storage will exceed the background loss from the methods of processing. Second, the unexpectedly good immediate survival after transfusion may reflect a selective population of cells. It is suggested that the loss of cells by lysis during processing may represent removal of red blood cells undergoing irreversible random damage during collection and processing.

Only 7 of the 100 units of blood stored at −120 C have been studied so far. These are insufficient data for comparison of optimal storage temperature. Due to the unanticipated high rate of survival of cells at −80 C, it may be a considerable period of time before any difference between the two storage temperatures will emerge.

In addition to the immediate post-transfusion survival, the subsequent rate of in vivo decay was followed in four cases where the patients remained in the hospital long enough to permit long-term follow-up study. These data (table 1) show that in two patients the disappearance of labeled cells

occurred at a normal rate of 50% in 30 days. In the other two patients, the rate was accelerated to 1.4 and 2.0 times normal. Each of the latter patients was a sick recipient. One received x-ray radiation to a total dose of 1,892 r during the one-month period his cell survival was being followed. The other was in a terminal phase of carcinoma of the intestine and blood loss into the gastrointestinal tract could not be excluded.

In vitro studies have shown oxygen-carrying capacity of the previously frozen erythrocytes to be entirely normal.

Supernatant Hemoglobin.—As noted earlier, post-processing storage of cells at ordinary refrigerator temperature is accompanied by a rising concentration of free hemoglobin in the supernatant solution surrounding the cells. Immediately after deglycerolization and resuspension of the cells, free hemoglobin is present in amounts totalling 150 mg.% (table 2). With storage, this level rises to an average of 240 mg.% at one week and 300 mg.% at two weeks. The amount of free hemoglobin which would be given in any single transfusion would be no greater than 10% more than these figures, as the supernatant phase of the concentrated red blood cells averages about 110 ml. As noted earlier, a recent change in experimental technique resulted in a marked reduction in the above figures for accumulation of free hemoglobin during storage at 4 C in the few instances when it was used. An aliquot of 30 ml. of autologous plasma with A. C. D. solution is saved during storage. Substitution of this for the standard resuspension medium has decreased hemoglobin liberation from twofold to fivefold. This relatively insignificant amount of hemoglobin can be reduced further, if desired, by the simple mechanical removal of the supernatant phase at the time of administration.

Plasma hemoglobin concentrations were studied at five minutes and 24 hours in 33 recipients of frozen blood. The average rise was 30 mg.% immediately after transfusion. In all cases this returned to pretransfusion levels in 24 hours. It is important to select an accurate and sensitive method for determination of plasma hemoglobin level for proper evaluation of studies of this type. The benzidine technique of Crosby and Furth [16] was used throughout this study except for the occasional instance where the amount of hemoglobin was high. In this case the technique of cyanomethemoglobin of Crosby and co-workers [17] was used. Resting pretransfusion recipient plasma hemoglobin levels averaged 20 mg.%, with one isolated reading as high as 60 mg.%. This is above the anticipated range for "normals" but probably was due to the various illnesses present in most of the recipients. Plasma bilirubin levels were occasionally tested three hours after transfusion and showed no rise secondary to the administered blood. Hemoglobinuria did not occur in any of the cases.

TABLE 1.—*Rate of in Vivo Decay of Red Blood Cells in Four Patients*

Case No.	Days Sampled, No.	Survival, %	T-½, Days	Rate of Disappearance
15	24	84	28	Normal
18	33	90	16	2 times normal
31	19	90	30	Normal
32	15	86	21	1.4 times normal

* T-½ value is expressed in days, being the day at which the unit activity (Cr^{51}) of red blood cells has fallen to 50% of the immediate survival value, as obtained by extrapolation.

TABLE 2.—*Supernatant Hemoglobin Levels, in Milligrams per 100 Cc., in Stored Resuspended Red Blood Cells*

Storage at ° C, Days	Experiment No. M604 Resuspension Medium	M628 Resuspension Medium	M561 (10% plasma)
1	150	176	28
3	215	270	50
7	280	310	96
14	380	500	150
21	500	520	210

Experimental injection into rabbits of hemoglobin, washed stroma, and hemoglobin-stroma mixtures, in concentrations ranging up to 100 times the maximum amount of hemoglobin which would be administered in the form of frozen red blood cells, have failed to disclose any deleterious effect or iron accumulation in analyzed organs. These data are the subject of a separate report.[18]

Summary

Human red blood cells processed in a closed-system Cohn centrifuge and stored in glycerol solution at −80 and −120 C have been transfused into recipients after preservation up to 19 months. The sterility of the system made possible an additional post-thawing storage of the cells up to 11 days at 4 C for distribution to the hospital in which the transfusions were administered. No transfusion reactions of any kind were noted. The cells appeared therapeutically comparable to cells in standard A. C. D. solution stored up to 21 days at 4 C.

281 South St. (30) (Dr. Tullis).

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The storage cabinets used in this study were designed, constructed, and maintained by the Harris Refrigeration Company, Cambridge, Mass.

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V. 1

USE OF BIOMECHANICAL EQUIPMENT FOR THE LONG-TERM PRESERVATION OF ERYTHROCYTES

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Human red blood cells can be stored for three months or longer at temperatures below −80 C if they are mixed with glycerol. Before the red blood cells can be used, however, they must be washed free of glycerol. Both the initial equilibration with glycerol before storage and the removal of the glycerol from the cells after storage involve fractional centrifugation. In order to accomplish this without bacterial contamination and with a minimum of hemolysis, the apparatus here described has been developed. Experience with 175 units of red blood cells so processed showed that sterility had been maintained, loss by hemolysis did not exceed 20%, and the time required for the processing had been significantly shortened.

The long-term preservation of erythrocytes has recently become possible because of the finding that the damage to erythrocytes caused by freezing and thawing can be greatly reduced if the cells are first equilibrated with a glycerol-containing medium.[1] Studies are available which indicate that erythrocytes preserved in this manner may be used in vivo.[2] However, the removal of glycerol before transfusion is done is a laborious and time-consuming process and is difficult to perform under sterile conditions. It appears that the removal of glycerol has provided the major obstacle to long-term storage of erythrocytes on a large scale.

From their studies with closed-system mechanical devices for the handling of blood, the attention of Cohn and his collaborators[3] was drawn to the possibility that the disadvantages of the glycerol

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method could be minimized if the processing were carried out in a closed system which imposed no limitation on the volume of solutions with which the cells could be washed. A centrifuge bowl designed for this specific purpose was first demonstrated in 1954.[4] These principles were later incorporated into an apparatus known as the Cohn ADL fractionator. This apparatus, which has been described in detail elsewhere,[5] contains two refrigerated, continuous-feed centrifuge bowls. Each bowl and the parts with which the blood comes in contact may be put in the autoclave as a unit, thus permitting operation without bacterial contamination. Evidence has been presented that human red blood cells collected and separated in the machine survive as well in vivo as cells collected by conventional blood bank methods.[6] With these semiautomatic methods, the time required for the removal of glycerol is shortened, the processing can be performed without bacterial contamination, the operator can work at comfortable temperatures while the cells are refrigerated, and the obvious advantages of mechanization are present.

Methods

With 75 ml. of A. C. D. solution (National Institutes of Health formula A) used as an anticoagulant, 500-ml. units of blood were collected into plastic blood bags. The solutions used to equilibrate the cells with glycerol and to remove glycerol from the cells (table 1) were prepared and stored according to accepted procedures for human in vivo use. Frequent bacteriological and pyrogenic tests were carried out.

TABLE 1.—*Composition of Solutions* Used in Equilibration of Red Blood Cells with Glycerol and in Removal of Glycerol from These Cells*

	Gm./Liter
Equilibration with Glycerol	
Solution A	
Glycerol†	500.0
Sodium lactate	29.2
Potassium chloride	0.3
Glucose	2.0
Removal of Glycerol	
Solution B	
Glycerol	100.0
Sodium lactate	97.2
Potassium chloride	0.3
Solution C	
Sodium lactate†	29.1
Potassium chloride	0.3
Solution D	
Sodium chloride	8.5
Resuspension Medium	
Solution E	
Albumin	50.0
Glucose	4.0
Potassium phosphate, dibasic	3.5
adjust to 0.15 with sodium chloride	
adjust to pH 6.9 with sodium bicarbonate	

* Solutions suggested by Dr. Ivan Brown, Duke University, Durham, N. C.

† Molarity of solution calculated from manufacturer's estimate of percentage of sodium lactate in the solution.

After thorough cleaning of the centrifuge cartridge, the disposable plastic parts and the bottles containing solutions were attached. The unit as a whole was put in the autoclave for 45 minutes at a pressure of 10 lb. per inch.[2a]

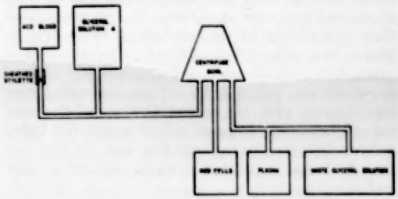

Fig. 1.—Schematic diagram of centrifuge cartridge assembly for equilibrating red blood cells with glycerol.

The plastic containers used throughout this study were equipped with plastic tubing projections. Thus, a sample of the contents of the containers could be removed, without risking contamination, by forcing some of the contents into the tubing projection and separating a length of the projection, by means of a dielectric sealer, from the container.

Equilibration of Cells with Glycerol Solution.—A schematic diagram of the centrifuge cartridge assembly for equilibrating the red blood cells with glycerol is shown in figure 1. A sheathed stylet, with which to connect the plastic blood bag and a bottle of glycerol solution share a common plastic tube which connects with the entry port of the centrifuge bowl. A plastic bag to receive the plasma during the red blood cell–plasma separation and a plastic bag to receive the waste glycerol solution are shown connected to a tube leading from the centrifuge bowl. After the washing operation is completed, the centrifuge bowl discharges its red blood cells into a separate plastic bag in which they are frozen. By sealing the plastic tubing and cutting through the seal, one may separate any of the plastic bags from the system without contaminating either the system or the contents of the bag. Slight pressures of nitrogen gas were used to force wash solutions into the centrifuge bowl. The rate of flow of blood or wash solution through the system was controlled by means of adjustable clamps on the plastic tubing. The vents for the system (not shown in diagram) were protected from bacterial contamination by means of filters.

The centrifuge cartridge, after being cooled in the fractionator, was set in operation at 5,000 rpm. With use of sterile technique, the plastic bag containing the blood-A. C. D. mixture was punctured with the sheathed stylet and the blood was forced by gravity to enter the centrifuge bowl at a rate of 50-60 ml. per minute. The red blood cells remained in the spinning centrifuge bowl, and the plasma was collected in its plastic bag.

The glycerol solution (solution A of table 1) was then allowed to enter drop-wise at a slow rate. The internal structure of the centrifuge bowl caused the glycerol solution to enter at the bottom of the bowl, rise through the cells, equilibrating with them, and spill over at the top. The waste solution then passed out of the centrifuge bowl into its plastic bag. After 100 to 200 ml. of solution A had washed the cells, the rate of flow could be increased to 40-50 ml. per minute. When the cells were equilibrated with the glycerol solution, the centrifuge bowl was stopped, allowing the red blood cells to fall into their plastic bag, and the bag was sealed off and separated from the centrifuge cartridge.

Refrigeration Equipment.—The cells were wrapped in aluminum foil as a protection against dehydration and were placed in a cardboard box to protect the plastic bag, which becomes brittle at low temperatures. The box was then placed directly in either of two storage cabinets maintained at −80 C ±2 and −120 C ±2. The −80 C unit has a

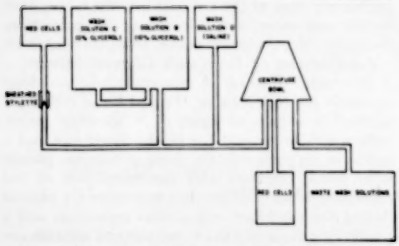

Fig. 2.—Schematic diagram of centrifuge cartridge assembly for removal of glycerol from red blood cells.

two-stage compressor system, with a storage capacity of 4.8 cu. ft. The −120 C unit has a three-stage compressor system with a storage capacity of 6 cu. ft. The cabinets were equipped with an automatic temperature recording device and an alarm system which warned of temperature rises. An auxiliary generator was available in the event of power failure.

Removal of Glycerol Solutions.—On removal of a unit of cells from the low-temperature cabinets, the plastic bag containing the cells was placed in a water bath at 37 C. As soon as the cells were thawed, the bag was punctured through a sterile sheath with a stylet, and the cells forced into the centrifuge bowl, which was spinning at 4,000 rpm. It is important that the cells be removed from the water bath as soon as they are thawed (about 15 minutes), in order to avoid cellular deterioration.

A schematic diagram of the centrifuge assembly for the removal of glycerol from the red blood cells is shown in figure 2. A sheathed stylet with which to connect the plastic bag containing the red blood cells and three separate bottles of wash solution share a common plastic tube which connects with the entry port of the centrifuge bowl. A waste bag to receive the used wash solution is shown connected to a tube leading from the centrifuge bowl. After the washing operation is completed, the centrifuge bowl discharges its contents of red blood cells into a plastic administration bag.

The tandem arrangement of the bottles containing wash solutions B and C (fig. 2) provided a gradual rather than an abrupt change in the tonicity to which the cells were subjected. As shown in table 1, solution B had a relatively high tonicity, while solution C was isotonic for red blood cells. When the cells were in the centrifuge bowl, solution B was allowed to enter drop-wise, and this rate could be gradually increased to 20 to 30 ml. per minute. After 1 liter of solution B had entered the bowl, a clamp between the bottles containing solution C and solution B was released. Thus, as each drop of solution B left its bottle, it was replaced by a drop of solution C. Since the density of solution C was less than that of solution B, the drops of solution C tended to rise. Finally, the remaining liter of solution C was washed through the cells.

When both solutions B and C had passed through the centrifuge, 1 liter of solution D (0.85% sodium chloride) was passed through. The centrifuge was stopped, and the cells dropped into a plastic container labeled "red cells" (fig. 2). This bag contained 60 ml. of solution E and the resuspension medium in which the cells were stored until transfused. Since this solution contained a protein, the bag in which it was contained was not put in the autoclave with the centrifuge cartridge but was attached, with use of aseptic technique, just before the centrifuge was stopped.

Determination of Glycerol Concentration.—The quantity of glycerol contained in the cell suspensions was determined by a modification of the spectrophotometric method of Karnovsky.[7] A sample of a red blood cell suspension which had not been equilibrated with glycerol was used as a blank, and the difference was attributed to the glycerol.

Determination of Cell Lysis.—The amount of a cell suspension which was lysed during processing was estimated by determining the amount of hemoglobin in the wash solutions. Hemoglobin level determinations in the wash solutions were made from readings on a Coleman junior spectrophotometer set at 455 mμ. A standard curve was plotted from dilutions of lysed red blood cells, and values of hemoglobin in unknown solutions were derived by comparison.

Bacteriological Studies.—Each unit of cells was tested for bacterial contamination after being equilibrated with glycerol and after removal of the glycerol. By sealing off a plastic tubing projection of the plastic container, it was possible to obtain a sample of the contents of the container without

danger of contamination of the remaining cells. For each sample tested, three Sabouraud's medium slants, three blood agar plates, and three tubes of thioglycollate glucose broth were inoculated. Cultures of each of the three mediums were incubated at 4 C, at room temperature, and at 37 C.

Results

The present report is concerned with units of red blood cells which were processed in the period from November, 1955, to July, 1956. During this time, 175 units of cells were frozen either at –80 or at –120 C. Fifty units have been used for in vitro evaluation studies. A separate report [8] is concerned with in vivo evaluation of these cells. The remainder of the units will be evaluated as they reach appropriate times in storage.

Bacteriological Studies.—In two cases, breaks occurred in the plastic storage containers due to the brittleness of the plastic at low temperatures. After the removal of glycerol, bacteriological testing produced positive cultures.

In tests made on 175 units of cells after equilibration with glycerol, and again on 47 of these units after the removal of glycerol, no further positive cultures were obtained. Further evidence of the absence of bacterial contamination during processing is obtained from the observation that no pyrogenic reactions occurred in patients receiving these cells.

Time Required for Processing.—The equilibration with glycerol of a unit of red blood cells requires from 45 to 50 minutes in the Cohn–ADL blood fractionator. The removal of glycerol requires from 90 to 120 minutes in the fractionator.

Recovery of Cells.—The percentage of cells which are lysed by the equilibration with glycerol and by the removal of glycerol was determined by a measurement of the hemoglobin level contained in wash solutions after the cells were processed. The results of such determinations both after equilibration with glycerol and after removal of glycerol are shown for three units of cells in table 2. The equilibration of the cells with glycerol resulted in a loss of from 1.1 to 1.8% of the total cells. From 9 to 12% of the total cells were recovered as hemoglobin in the wash solution used to remove the glycerol from the cells. It should be emphasized that this latter loss not only is a result of the removal of glycerol but also includes the loss of those cells which are lysed or injured by freezing and thawing. Since the units recorded in table 2 were in storage for one month or less, losses occurring as a result of length of time in storage are not a factor.

Losses of cells as intact cells, when being transferred from container to centrifuge bowl, and in other transfers, as cells used for cross-matching and serology, and as cells used in bacteriological testing account for approximately 8 to 10% of the original cells. Added to the losses occurring as a result of equilibration with glycerol and removal of glycerol, a total loss of approximately 20% of the cells occurs.

Removal of Glycerol from Cell Suspension.—Samples of eight units of cells were tested after the removal of glycerol to determine the amount of glycerol that was not removed from the cells by the processing. In all eight units, the glycerol content was found to be less than 1 Gm. per 100 cc.

Reliability of Refrigeration Equipment.—A constant consideration during the course of these experiments concerned the feasibility of maintaining the temperatures of –80 and –120 C, at which the cells are stored. Three failures of the equipment occurred. In one, a power failure in the lines of the local utility company resulted in a rise in temperature to –60 C. A further rise in temperature was prevented by placing solid carbon dioxide in the storage cabinet. Recurrence of this type of failure has been prevented by the installation of an emergency generator.

In two other failures mechanical breakdowns occurred in the compressors. The prompt attention of mechanics prevented these failures from resulting in significant temperature rises. It is unnecessary to open the storage cabinets in order to repair the compressors, so the heavy insulation of the cabinets prevents rapid rises in temperature when mechanical failures occur.

TABLE 2.—*Percentage of Cells Lost in Each Stage of Processing*

Time in Storage, Days	Equilibration with Glycerol	Removal of Glycerol*	Total
1	1.8	10	11.8
7	1.8	12	13.8
30	1.1	9	10.1
Total			35.7
Av.			11.9

* Including cells hemolysed by freezing and thawing.

No special significance was attached to the temperature at which cells were stored in these experiments. Since much work on the freezing of cells has been carried out at the temperatures of solid carbon dioxide, one cabinet was designed so that it would operate near –79 C. The cabinet was found to run at –80 C and was not adjusted. The temperature of –120 C was chosen in conference with the manufacturer of the equipment as his estimate of a temperature which could be obtained with practical equipment.

Comment

The principal objective of this study was to establish a set of results, obtained from a sufficient number of experiments, against which future improvements in the present method could be compared. Future reports concerning the cells now in storage will add more such data. The composition of the wash solutions, the volume of wash solutions, and the rate of washing might all be modified so that a shorter time for processing and improvement in the number and quality of recovered cells would result.

In the present study, 90 to 120 minutes in the Cohn ADL blood fractionator was required to remove the glycerol from each unit of cells. This is a considerable reduction in the time required by conventional centrifuge methods. The standard model of the Cohn ADL blood fractionator consists of two centrifuge units, and, whenever required in the present study, two units of cells were processed in the machine simultaneously by the same operator, thus reducing the unit time by one-half. If a large-scale program were considered, a series of centrifuge units could be arranged so that a trained operator and an assistant would be able to process a large number of units simultaneously. In this manner, the time required per unit of cells could be greatly reduced.

Perhaps of significance to others interested in low-temperature storage is the record of performance of equipment operating at –80 and –120 C. Power failures can be met by an emergency generator. Placing the mechanical parts of the equipment in a position so that they can be repaired without opening the storage cabinet takes advantage of the heavy insulation in slowing the temperature rise. Although full confidence must await longer trials, performance in our laboratory indicates that temperatures as low as –120 C may be maintained satisfactorily for long periods.

Summary

A method for the equilibration of red blood cells with glycerol and for the removal of glycerol from these cells, utilizes the Cohn ADL blood fractionator. In periods of storage from one day to three months, an average of 80% of the donor cells were available for transfusion into three recipients. Except in known instances of breaks in sterility, no bacterial contamination was observed.

The equilibration of a unit of cells with glycerol requires 45 to 50 minutes in the Cohn ADL blood fractionator, and the removal of glycerol requires 90 to 120 minutes. Temperatures were adequately maintained at –80 C and –120 C with mechanical equipment. Losses of cells from equipment failure did not occur.

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This study was carried out under contract with the Office of Naval Research, Department of the Navy, with funds supplied by the research and development departments of the U. S. Navy, Army, and Air Force.

The storage cabinets used in this study were designed, constructed, and maintained by the Harris Refrigeration Company, Cambridge, Mass.

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PEPTIC ESOPHAGITIS.—Cholecystectomy for cholelithiasis was performed in four patients without relief of symptoms. In one patient, subsequent sphincterotomy for a presumptive diagnosis of biliary dyskinesia also failed to relieve the symptomatology. Gastroenterologic examination from one to eight years later revealed hiatus hernia (sliding) with peptic (reflux) esophagitis. Medical therapy produced symptomatic relief in three patients, while one required surgical intervention for repair of the hernia. The "postcholecystectomy syndrome" is in some instances a result of inadequate preoperative investigation. Peptic esophagitis may be responsible for the symptoms of a patient with calculous disease of the gallbladder whenever heartburn and sour regurgitation appear prominent in the clinical picture. In these patients the decision to operate for gall-bladder disease should be an indication for barium meal study. The high incidence of silent, calculous gallbladder makes such clinical investigation mandatory to avoid some of the failures of gall-bladder surgery.—A. I. Friedman, M.D., Peptic Esophagitis Simulating the "Postcholecystectomy Syndrome," *Annals of Internal Medicine*, July, 1958.

CLINICAL NOTES

TUBELESS GASTRIC ANALYSIS

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The tubeless detection of gastric acidity, as developed by Segal and associates,[1] makes it possible to ascertain the state of gastric acidity in specific cases or in mass screening examinations without the use of complicated or cumbersome chemical procedures. The rationale of tubeless analysis depends on the use of a dye, azure A, which is released from a cation exchange resin by free hydrochloric acid in the stomach. In the presence of free acid, the free dye is absorbed and consequently excreted in the urine and the blue color of the urine may then be visually compared with a solution of azure A of known concentration.

It has been reported by other workers [2] that in about 50% of the tests the azure A is excreted in a reduced, colorless form that requires oxidation with acid and heat to bring out the color. In our experience, about 75% of the positive samples require oxidation. Since azure A is a thionine dye similar to methylene blue, it is easily reduced with ascorbic acid in acid or alkaline solution. The presence of ascorbic acid and reductone in urine is probably responsible for the excretion of azure A in the colorless, reduced form. The ease with which ascorbic acid reduces the azure A makes it possible to use the test urine sample as its own control, thus eliminating the collection of a control sample.

Methods and Materials

The highly satisfactory modified test, in use in this laboratory for about one year, is as follows: Patients in the fasting state are given two tablets (0.5 Gm.) of caffeine and sodium benzoate by mouth with one-half glass of water. The patient is permitted to urinate at will. One hour later, the bladder is emptied and the urine discarded. The patient is given the azure A granules with one-half glass of water, and all the voided urine is collected for the next two hours.

For analysis, the urine sample is diluted to 300 ml. To about 15 ml. of the diluted sample in a large test tube, two drops of oxidizing reagent (200 mg. of copper sulfate in 100 ml. of 18% hydrochloric acid) are added; this is placed in a boiling water bath for 10 minutes. It is then allowed to cool to room temperature for two hours. Samples that are not obviously positive are divided into two portions in test tubes. To one tube a pinch (300 mg.) of ascorbic acid is added and mixed to reduce the dye. The oxidized and reduced samples are compared with the 0.3-mg. and 0.6-mg. azure A standards.

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Results

In 32 patients who secreted free hydrochloric acid and in 10 with hypochlorhydria or achlorhydria, most of whom were ambulatory, the simplified procedure yielded results identical with the more complicated control and test urine sample technique. Since the test sample contains the pigments of urine collected over a two-hour period, as compared with the one-hour control sample, most of the test samples, reduced with ascorbic acid, appeared darker than the control.

In three other cases the diagnosis was altered from hypochlorhydria to achlorhydria when the test sample was used as its own control. In one patient with proteinuria, the azure A test was obviously invalidated and required standard intubation techniques for evaluation.

Conclusions

As a mass screening procedure for the diagnosis of pernicious anemia, gastric cancer, and duodenal ulcer, the tubeless analysis for gastric acidity is a useful technique. The elimination of the control sample simplifies the procedure in that one urine sample serves for both the test and the control. For the busy clinic, hospital, or office, a single urine sample decreases the effort of monitoring samples on many patients. In addition, the single urine collection makes instructions to the patient simpler and avoids the need for retesting due to inadequate sampling.

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The azure A resin compound used in this study was supplied as Diagnex Blue by E. R. Squibb & Sons, New York.

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POTENTIATION OF ANTIHYPERTENSIVE THERAPY BY USE OF CHLOROTHIAZIDE

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Although chlorothiazide (Diuril) was initially introduced as an orally given diuretic,[1] subsequent clinical trial readily revealed this agent to possess significant antihypertensive properties. In 25 patients moderate hypertension had been somewhat less than adequately controlled for a period of at least six months with Rauwolfia (Raudixin) alone. In another 25 patients it had been inadequately controlled for a similar period with a regimen of Rauwolfia and mecamylamine (Inversine). Chlorothiazide (500 mg. after breakfast and lunch) was added to the therapeutic regimen of each patient.

In the first group of patients, the upright mean blood pressure was reduced from the control level of 131 mm. Hg to 109 mm. Hg ($p<0.01$) after 12 weeks of chlorothiazide therapy. A contemporary decrease in body weight became significant at the end of 12 weeks (table 1). In the group of patients receiving a drug combination of Rauwolfia and mecamylamine, the mean blood pressure in the upright position was reduced from the control value of 139 mm. Hg to 102 mm. Hg ($p<0.001$) after 12 weeks of chlorothiazide therapy. A contemporary decrease in body weight occurred (table 1).

TABLE 1.—*Average Effect of Chlorothiazide in Augmenting Antihypertensive Therapy in Two Groups of Patients**

	Blood Pressure, Mm. Hg†			Wt., Lb.	p Value‡
	Lying	Standing	p Value‡		
Twenty-five Patients Receiving Rauwolfia					
Control period	188/108(135)	174/110(131)		172	
After 3 wk. of therapy	170/99 (123)	155/96 (116)	<0.01	171	NS
After 6 wk. of therapy	160/95 (117)	148/91 (110)	<0.001	171	NS
After 12 wk. of therapy	166/93 (117)	147/90 (109)	<0.001	171	<0.01
Twenty-five Patients Receiving Rauwolfia and Mecamylamine					
Control period	201/121(148)	169/109(139)		160	
After 3 wk. of therapy	182/110(134)	150/97 (115)	<0.001	160	NS
After 6 wk. of therapy	172/104(127)	139/93 (109)	<0.001	159	<0.01
After 12 wk. of therapy	167/102(124)	132/87 (102)	<0.001	158	<0.01

* Chlorothiazide given in dosage of 500 mg. twice daily orally.
† Numbers in parentheses give mean blood pressure, which equals diastolic plus one-third pulse pressure.
‡ p Value derived from Student's "t" test applied to standing mean blood pressure between drug and control periods.

With addition of chlorothiazide to the Rauwolfia antihypertensive regimen, approximately 20% of the patients evidenced a decrease in blood pressure associated with a gain in weight, while the largest group of patients (41%) showed a decrease in blood pressure associated with either a steady weight or slight weight reduction as a manifestation of diuresis (table 2). The correlation of body weight changes and the changes in blood pressure associated with addition of chlorothiazide to the combination Rauwolfia–mecamylamine antihypertensive regimen was essentially the same as with the former group (table 2).

Comment

Although the results of this study further define the hypotensive properties of chlorothiazide, the fundamental problem of the mechanism of this response is still not fully apparent. We [2] have recently shown that the potentiation of antihypertensive agents is a property common to all effective diuretics and that the degree of potentiation seen is a reflection of the relative potency (as manifested by enhanced sodium excretion as well as decreased body weight) of the diuretic. It would appear that the encouraging results to date with chlorothiazide in the treatment of hypertension are due to the fact that it has a high relative diuretic potency and continues to be effective on repetitive administration. Though a direct antihypertensive effect cannot be excluded, present evidence suggests that the blood pressure responses seen with the use of chlorothiazide in hypertension are a result of its diuretic effect.

TABLE 2.—*Correlation of Changes in Blood Pressure and Body Weight in Antihypertensive Regimens After Addition of Chlorothiazide*

	Rauwolfia		Rauwolfia-Mecamylamine	
	No.	%	No.	%
Increase				
Wt. gain	3	4	6	8
No wt. gain	6	8	7	9
Decrease				
Wt. gain	15	20	12	16
No wt. gain	31	41	30	40
No change				
Wt. gain	5	7	4	5
No wt. gain	15	20	16	22
Total*	75	100	75	100

* Observations on 25 patients in three drug periods.

2002 Holcombe Blvd. (31) (Dr. Ford).

The chlorothiazide used in this study was supplied as Diuril, and the mecamylamine as Inversine by Merck Sharp & Dohme Research Laboratories, West Point, Pa.; the Rauwolfia used, as Raudixin by E. R. Squibb & Sons, New York.

From the departments of medicine and pharmacology, Baylor University College of Medicine and the Medical Service of the Veterans Administration Hospital.

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ANOMALOUS CASE OF EDEMA, ANASARCA, AND POLYSEROSITIS

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Recently, we have had occasion to study another case of anomalous edema, characterized by a slowly progressive downward course ending in anasarca, polyserositis, and death. The diagnosis in life was indeterminate despite several months spent in the hospital and innumerable laboratory tests. Clinical studies and autopsy examination excluded all the ordinary causes of edema (diseases of heart, liver, kidneys, and blood) and also more unusual syndromes.

It is thought that this case may represent a new syndrome similar in part to three others previously reported by one of us,[1] representing a disease that is the antithesis of diabetes insipidus, characterized by salt and water retention and postulated as possibly due to "hyperpitressinism." If it does, then it represents a fulminating form of the same, and our first autopsy report of such a case.

Report of a Case

A 39-year-old female had noted gradual onset of periorbital, scalp, and ankle edema in the fall of 1954. Her weight rose from 135 lb. (61.2 kg.) in September, 1954, to 155 lb. (70.3 kg.) in February, 1955. She had noticed no change in thirst, desire for salt, frequency of urination, or marked fluctuations in her edema or weight. In 1937 her left fallopian tube and an ovarian cyst had been removed. For two years her menstrual periods had been irregular, and for one year she had had infrequent "hot flashes." In January, 1955, her local doctor had informed her of a "left pelvic mass."

On her initial hospitalization in February, 1955, she displayed edema of the scalp, periorbital areas, and ankles. Physical examination was otherwise negative except that attempts at pelvic examination were unsuccessful. The patient's blood pressure was 118/72 mm. Hg. Abnormal levels of blood pressure were never obtained.

Numerous laboratory studies were performed, with normal results being obtained (see table). Her edema partially subsided, and she was discharged from the hospital in April, 1955, weighing 149 lb. (67.6 kg.).

While at home she had gradual weight gain without noting change in water or salt intake or urine output. On readmission to the hospital on June 12, 1955, she weighed 168 lb. (76.2 kg.). Edema of the face and scalp, distended cervical veins, engorged breasts, bilateral pleural effusion, ascites, and marked edema of the lower abdominal wall and lower extremities were present. The heart sounds, rate, and rhythm were normal. Pelvic examination was again unsatisfactory.

Until her death on Jan. 7, 1956, there was slowly progressive anasarca, with distressing accumulations of fluid in serous cavities and subcutaneous tissue. Repeated laboratory diagnostic studies were performed without a clue as to diagnosis. Pleural, pericardial, and peritoneal fluid was removed on several occasions, in total amount over 20 liters; the fluid was normal on cytological, culture, and smear study, as well as on study of several guinea pig inoculations. Catheterization of the right side of the heart was performed on Nov. 10, 1955, at the National Children's Cardiac Hospital. Findings failed to reveal any disturbance in measurable cardiac physiology.

Attempts to control the fluid accumulation with the usual diuretic measures (ammonium chloride, acetazolamide [Diamox], potassium chloride, mercaptomerin [Thiomerin] sodium, and meralluride [Mercuhydrin] sodium) were at times transiently and only partially successful. Digitalization on two occasions and administration of ACTH and prednisone on other occasions were without apparent benefit. Gradually all diuretic measures were to no avail, and she became weaker and apathetic; without developing new signs or symptoms she lapsed into coma and died on Jan. 7, 1956.

Laboratory Data.—During her hospitalization the patient had many laboratory studies performed, and the laboratory data are summarized in the table. Her urinary sodium output

Laboratory Data of Patient with Edema Followed by Anasarca and Polyserositis

Test	During First Admission	During Second Admission
Hemoglobin level, Gm. %	13.5	13-15.5 (range of 11 determinations)
White blood cell count, per cu. mm.	9,450, normal differential	7,650-16,250 (range of 13 determinations); normal differential
Urine: specific gravity	1.016	1.002-1.022 (range of 17)
Albumin	Negative	Faint trace (maximum of 17)
White blood cells per high-power field	0-2	1-3-10-15 (range of 17)
Sugar	Negative	Negative
24-Hr. protein, mg.	...	50-136 (range of 5)
Maximum concentration	1.018	...
Maximum dilution	1.001	...
Sodium excretion, mEq./24 hr.	...	3.13-312
Potassium excretion, mEq./24 hr.	...	3.74-172
Chloride excretion, mEq./24 hr.	...	25.3-492
Phenolsulfonphthalein excretion, min.	18% at 15; 30% at 30	...
Urea clearance, % of normal	82	39 (9/13/56)
Urine culture	Negative	Negative five times
Serum calcium level, mg. %	11	...
Serum phosphorus level, mg. %	4.2	...
Serum bilirubin level, mg. %	...	0.6
Urea nitrogen, mg. %	17	6-22 (range of 15)
Thymol turbidity, units	...	2.5
Cephalin flocculation	...	Negative in 48 hours
Cholesterol, mg. %	254	175
Alkaline phosphatase level, Bodansky units	...	4.6
Prothrombin time, % of normal	...	100
Congo red, % absorption in 65 min.	...	23
L. E. cells	...	Negative four times
Sodium, mEq./liter	...	135-136 (range of 17)
Potassium, mEq./liter	...	2.47-6 (range of 17)
Chloride, mEq./liter	...	90-107 (range of 17)
CO_2, mEq./liter	...	29-36 (range of 17)
Culture for fungus and acid-fast organisms of pleural fluid	...	Negative four times
Thyroid I^{131} uptake, % at 24 hr.	19 (euthyroid)	
Electrocardiogram	Normal	Low voltage T waves, consistent with anasarca
Roentgenologic studies:		
Chest	Within normal limits	Bilateral pleural effusion
Skull	Normal	
Intravenous pyelogram	Within normal limits	

From the medical service, Veterans Administration Hospital (Drs. Rowntree, Winter, and Brown) and the Howard Hughes Medical Institute (Dr. Boucek).

for a three-week period during her last admission varied from 0.13 mEq. per 24 hours to 312 mEq. per 24 hours. There were similar wide ranges in potassium excretion (from 3.74 mEq. per 24 hours to 172 mEq. per 24 hours) and chloride excretion (from 25.3 mEq. per 24 hours to

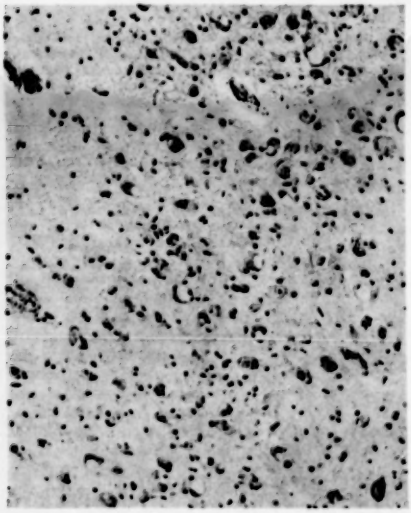

Fig. 1.—Low-power view of supraoptic nucleus, showing numerous vacuolated nerve cells (hematoxylin-eosin stain, × 136).

492 mEq. per 24 hours). The low values coincided with episodes of oliguria and weight gain (water retention), while the high values occurred after the administration of diuretics and consequent diuresis. Electrocardiograms showed low voltage consistent with marked edema.

Repeated chest x-ray examinations showed massive bilateral hydrothoraces, which varied with thoracentesis and a presumed hydropericardium. Biopsy of the gum was normal. Biopsy of the skin from the legs was normal. Biopsy of the upper abdominal skin was normal; except for a small vein with an organized thrombus, no diagnosis could be made. Results of repeated Congo red tests for amyloidosis were negative.

Autopsy.—The following gross findings and microscopic findings were made at autopsy.

Gross Findings: The body was well developed but there was an extreme degree of waterlogging of the subcutaneous tissue of the upper and lower extremities and the trunk, so much so that each incision became immediately the site of an outpouring of water. There was no edema of the face. The breasts were atrophic. Approximately 2,000 ml. of turbid fluid was present in each pleural cavity and 500 ml. of dark brown fluid in the pericardial sac. Clear serous fluid (1,500 ml.) filled the peritoneal cavity. Both lungs were pushed upward and the lower lobes were almost completely collapsed. There was very little edema of the upper lobes. The pericardial sac was thickened, and a delicate ball and chain–like fibrinous adhesion was attached to the anterior wall of the left ventricle. Showers of petechiae were distributed about the base of the heart. The myocardium, valve leaflets, and coronary arteries were normal. The pelvic cavity was considerably obliterated by old adhesions in which the cervical stump of the uterus was embedded. A nodular mass, containing several small multiloculated cysts, some filled with old blood, and a shrunken ovary occupied the left parametrium. The thyroid and adrenal glands were grossly normal. Several small shallow ulcers were found in the duodenum overlying the head of the pancreas. The liver, pancreas, spleen, and kidneys showed no gross abnormalities. The gross appearance of the brain was normal.

Microscopic Findings: Many of the nerve cells in the supraoptic and paraventricular nuclei of the hypothalamus contained large cytoplasmic vacuoles which distended and distorted the cell bodies, often displacing the nuclei to the periphery (fig. 1). In some of the vacuoles, a pale colloid-like material, which stained faintly with hematoxylin-eosin stain and Gomori's chrome-alum hematoxylin stain, was visible (fig. 2). An occasional cell in the paraventricular nuclei contained a single large red cytoplasmic droplet seen only with the Gomori stain. Basophilic cytoplasmic granules morphologically similar to neurosecretory material were

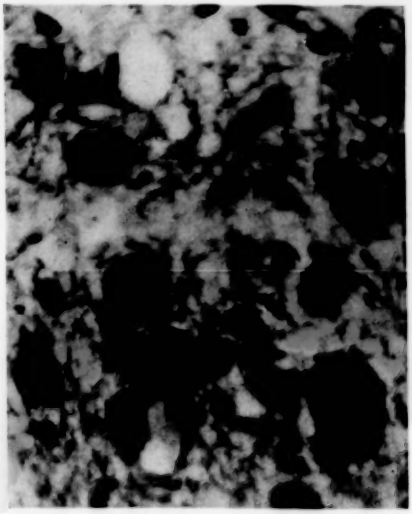

Fig. 2.—Supraoptic nerve cells, showing colloid-like material within cytoplasm and vacuolation (hematoxylin-eosin stain, × 435).

demonstrated with the Gomori stain in many, but not all, of the nerve cells in the supraoptic nuclei. These bore no relation to the cytoplasmic vacuoles. Histologically, the pituitary appeared normal, and scattered coarse basophilic droplets were demonstrated in the posterior lobe with the chrome-alum hematoxylin stain.

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V. 1

Since the vacuolar changes in the supraoptic nuclei were so pronounced in this case, an attempt was made to compare the incidence of such changes in these nuclei with changes in patients with edema of known etiology. In five patients with portal cirrhosis with severe ascites and one patient with chronic glomerulonephritis with anasarca no such vacuolar changes were found in the supraoptic nuclei. On the other hand five autopsied patients who died of carcinoma, cerebral arteriosclerosis, and lymphoma without edema showed vacuoles in the supraoptic nuclei, but only within a very few cells in each patient. The significance of the marked vacuolation in this case was, of course, obscure, but the impression was gained that there was some relation, perhaps causal, to the profound disturbance in water and salt balance. In support of this idea is the observation of Leveque,[2] who described somewhat similar vacuolar changes in the supraoptic nuclei of rats subjected to sodium chloride overloading.

In the atelectatic portions of the lungs the alveolar walls were somewhat thickened by an increase of the reticular fibrils. The liver architecture was normal. The thyroid showed variation in size of acini, most being small and containing poorly stained, granular and inspissated colloid, while the lining cells were low and cuboid. Histologically, the adrenal was normal; the cells of the zona fasciculata were filled with lipid. The bone marrow had a normal cellularity, although there was a definite increase of eosinophilic granulocytes. The kidney structures were normal, except for an albuminous exudate in many of the glomerular spaces. The stump of the uterus was lined by atrophic endometrium. The left ovary contained a number of corpora albicantia, one of which was cystic and filled with old blood pigment. The peritoneal surface was thickened with fibrous tissue.

Comment

Diabetes insipidus is thought to be due to a deficiency of the secretion of the antidiuretic hormone, emanating from the neurohypophysis.[3] A documentary proved case of hypersecretion of the antidiuretic hormone by the neurohypophysis has yet to be reported. However, in a recent case reported by us,[1b] the suggestion was made that fluid and salt retention noted in a patient as a late complication of encephalitis may have resulted from an oversecretion of this hormone and in reality be the antithesis of diabetes insipidus. In 1922, 1929, 1933, and 1943 various authors [4] have reported upon anomalous water and salt retention and suggested that these may have represented the antithesis of diabetes insipidus.

In our recently reported case [1b] evidence was presented suggesting a disturbed red blood cell, sodium, and potassium relationship. It was suggested that the "redox sodium pump mechanism" (oxidation-reduction cycle) might be influenced by a neurohypophysial lesion. Recently, Friedman and co-workers [5] have demonstrated that the administration of vasopressin (Pitressin) to nephrectomized rats caused a movement of sodium and water into cells, accompanied by a loss of cellular potassium, indicating a cellular membrane response to vasopressin. The cellular electrolyte aberrance induced in rats by the administration of vasopressin was similar in many respects to that which we reported existing in our patient with postencephalitis and representing a possible antithesis of diabetes insipidus. The case included in this report may represent a variation of this syndrome. Hydrocatochosis might be used as a general term signifying water retention in the body. The case reported would be classified as hypothalmic hydrocatochosis. The secretory granules containing the antidiuretic hormone are formed in the cells of the supraoptic nuclei and presumably transmit the material through the stalk of the posterior pituitary gland, where it is stored.[6] The widespread histological changes noted in the neurosecretory cells of the hypothalamus may be of primary importance in the etiology of this patient's disturbed salt and water metabolism.

Conclusions

In a patient with anomalous edema, the condition ran a downward course, ending in generalized anasarca and polyserositis. Autopsy excluded all the commonly recognized diseases associated with edema. Marked histological changes which may possibly be of pathogenic significance were encountered in the cells of the supraoptic nuclei.

1241 DuPont Bldg., Miami 32 (Dr. Rowntree).

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"FREE CHOICE" AND OTHER LIMITATIONS UNDER MEDICARE

EFFECTIVE midnight Tuesday, September 30, many dependents of military personnel will no longer be eligible to receive certain categories of medical and hospital care from civilian physicians and hospitals at government expense. Physicians should take note of these changes so that they will know beforehand which treatments will be eligible for payment under the Medicare system and which must be paid for by the individual patient.

On and after October 1, 1958, the government will no longer pay for the following items when provided outside military facilities: (1) treatment of fractures, dislocations, lacerations, and other wounds on an outpatient basis; (2) termination visit; (3) outpatient presurgical and postsurgical tests and procedures; (4) neonatal visits; (5) treatment of acute emotional disorders unless the patient (spouse or child) is confined to a hospital for a condition otherwise eligible for payment; (6) elective surgery.

In addition to eliminating these six categories of civilian care completely, the new directives further restrict the number of dependents eligible to receive any treatment from civilian physicians in nongovernmental hospitals.

Dependent spouses and children not residing with their sponsors may continue to choose a civilian physician, providing it is for treatment authorized for payment under the amended regulations.

However, dependents residing with their sponsors will be required first to check with the nearest medical facility of the uniformed service to ascertain whether the authorized care is available in that installation. If the facility is declared adequate by the appropriate local Command, the dependent must receive treatment at that facility or else assume the responsibility of paying for the care. Only if this designated local Command deems the facility inadequate for the necessary authorized care is a permit issued for the dependent to receive care from civilian sources at government expense. Except in emergency cases, this permit must be attached to the original copy of Claim form DA 1863, initiated by the physician in charge of the treatment.

In maternity cases, special provisions apply. A dependent living with her sponsor who is already in the second or third trimester on October 1 and is under the care of a civilian physician may continue under his care. However, if she is still in the first trimester on that date, she also must get the special permit to continue with civilian care.

All changes take effect on October 1, 1958. In some cases, however, categories of care discontinued by this directive may still be eligible for payment if hospitalization commenced or care was arranged for before the effective date.

Details of the new restrictions did not reach THE JOURNAL office in sufficient time for a more complete article. A more complete report together with some of the background information will be carried in the next issue of THE JOURNAL.

ANOTHER MEDICAL GUIDELINE

Simply to see or not to see represents a stark and shadowless difference between sight and blindness. On the other hand, significant gradations and colors in the efficacy of the visual system too often emerge ill-defined and blurred as the physician tries to interpret scientific finding in the light of professional judgment. This he has been doing in appraising visual impairment that is congenital or brought on by injury or disease.

How does a person's visual deficiency influence his ability to live a normal life? How do you evaluate the degree of impairment of this ability? For many years doctors and laymen have tried to answer these questions in efforts to bring about equitable decisions by such organizations as the Veterans Administration, insurance firms, the Social Security Administration, and workmen's compensation boards.

The medical profession now has a new gauge. This is a guide to the evaluation of permanent impairment of the visual system, which appears as a special article on page 475 of this issue of THE JOURNAL. It is the second such guide to be produced by the A. M. A. Committee on Medical Rating of Physical Impairment since that Committee was established by the Board of Trustees two years ago. The first, dealing with the extremities and the back, was published as a special edition of THE JOURNAL last February 15. Both guides were developed after the Committee and its outstanding consultants spent many months surveying the respective fields. Both guides will be reviewed from time to time to insure their continued value as advances in medical knowledge and technique occur.

While the guides should prove valuable to specialist physicians and interested nonmedical groups, they have been prepared with the general medical practitioner in mind. For it is the family doctor who is being called on increasingly to provide medical data for applications for disability benefits, and who stands to benefit greatly from uniform standards of impairment evaluation. For the past 18 years the A. M. A. has been striving to meet this need in a growing society—in 1940 adopting a recommendation of its Section on Ophthalmology on appraisal of loss of visual efficiency, in 1955 revising that pioneer report, and now bringing the information up to date in easy-to-use form.

This latest guide seeks to provide a simplified method for determining visual impairment and the extent of its effects on an individual's ability to perform the activities of daily living. Diminished visual ability is expressed as a percentage of impairment of the visual system. Diminished ability of the individual is expressed as a percentage of impairment of the "whole man." Using these values, the physician will have a practical means for expressing and calculating the extent of permanent impairment and for encouraging accurate, equitable, and uniform evaluation. Thus lay administrators should be able to pronounce proper judgment on a permanent disability. The doctor's responsibility is to evaluate a patient's impairment.

As the A. M. A. Committee continues its trailblazing work, it will present similar guides (covering the cardiovascular system, respiratory conditions, and other body systems) in future issues of THE JOURNAL. Reprints of the guide published today are available on a complimentary basis from the Committee at A. M. A. headquarters.

HYPOPHOSPHATASIA

Hypophosphatasia, a relatively rare condition, has been defined as an inborn error of metabolism characterized by abnormal mineralization of bone, diminished alkaline phosphatase activity, and increased urinary excretion of phosphorylethanolamine. One of the reasons it has been so rarely reported is that some cases have undoubtedly been thought to be rickets. Although no accurate estimate of the prevalence of the disease can be made, Fraser [1] believes it to be about one in every 100,000 live births. The disease is hereditary and close relatives even though they may show no outward signs of the disease are usually found to have a low phosphatase activity. When the condition is present at birth, failure to grow, vomiting, irritability, and constipation are commonly noted.[2] In general the later in life the disease is discovered the better the chances for recovery. There is a deficiency of calcification and as a result the growth of long bones is impaired and spontaneous fractures may occur in severe cases. Since early growth of the skull is retarded craniostenosis may develop as the child grows older. This in turn may cause convulsions and defective vision. Blindness may ensue if surgical measures are not taken to prevent it.[3] The primary teeth may be lost prematurely due to inadequate growth of alveolar bone and incomplete formation and early resorption of the roots of the teeth.

Although resembling rickets in many respects hypophosphatasia is in no way related to rickets, which is not hereditary and is not characterized by an absence of alkaline phosphatase (in rickets the phosphatase activity is normal or increased), hypercalcemia, or multiple spontaneous fractures. The histological differences are minor. In sections of rachitic bone osteoclasts are rarely seen and spicules of the substantia spongiosa are well ossified. Furthermore rickets does not affect the skull. One of the chief distinguishing features of hypophosphatasia is that vitamin D in adequate doses gives no improvement. Hypophosphatasia also usually has an earlier onset and may even occur in utero. Signs of rickets are rare in the fetus or newborn infant, occurring only when the mother had severe osteomalacia during pregnancy.[4]

Fraser grouped a series of 35 patients according to the age of the patient when the disease was discovered and concluded that if lesions are present at birth the patient will usually die within a few months. If an infant with this condition survives his first year his chances for recovery are good. In those who die renal calcinosis due to hypercalcemia is found but it is not certain that this is the principal cause of death. In patients with idiopathic hypercalcemia, however, higher levels of serum calcium are seen but are not associated with serious or permanent renal damage. If lesions appear after the child is 6 months old symptoms may gradually subside. Wide variations were observed in the rate and extent of healing. In a few patients the condition was first recognized in adult life. These patients had undue fragility of their long bone and radiologic evidence of a mild osteoporosis. In any case once healing of the bones occurred no relapses were reported but return of serum phosphatase levels to normal did not occur. Life expectancy in those with mild hypophosphatasia is probably normal. Many drugs have been used to treat this condition without success. Vitamin D should not be used because it favors hypercalcemia. Cortisone has been tried but no definite conclusions as to its value are warranted at present.

Hypophosphatasia appears to be the result of a disturbance in cellular processes concerned with either the elaboration of the organic matrix of bone or its calcification, or both. An understanding of the intrinsic disturbance in this condition should give us a better appreciation of the basic physiology of bone.

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THE PRESIDENT'S PAGE

A MONTHLY MESSAGE

Medicine recently has been much concerned by what is called "third parties." A third party has been defined as any mechanism which enters into the relationship between the patient and his physician. In this page I confine my remarks regarding third parties to closed panel (1) union, (2) management, and (3) consumer sponsored plans and exclude medical society sponsored Blue Shield plans and commercial insurance.

Third party arrangements of these three types—for prepaying the cost and for the provision of medical care—date back more than 100 years. Those of more recent origin are the closed panel plans such as the Health Insurance Plan of New York and the Kaiser Health Foundation, and the some 50 union health centers throughout the United States. The union health and welfare program which has generated the most controversy is the United Mine Workers program covering one million members and dependents in 25 states.

The American Medical Association has not opposed these third parties as such, but it has expressed concern that an adverse effect on the selection of physicians, their compensation, and the quality of medical care rendered might occur because of the third parties' methods of operation and financial interest.

While the medical profession has been striving to attain full acceptance of the fundamental principle of the individual's right to choose his own physician, certain third parties in recent years have moved in the opposite direction. They arbitrarily select physicians for their members and require the members to use their services exclusively or pay for the services of another physician.

This abridgment of the patient's freedom of choice often occurs because of the third party's special interests. Likewise, methods of compensation other than fee-for-service, establishment of inequitable professional standards, and limitation of diagnostic and treatment services may be stimulated because of fiscal considerations rather than the needs of the patient or physician. In some plans promotional techniques may be developed that conflict sharply with traditional ethical methods for establishing a medical practice.

The interests of the patient and his medical care must come first. The patient must not be a pawn or captive of a third party. He should be free to select his own physician because that choice, in my opinion, is essential to the provision of the best medical care. Certainly experience has taught us that free choice generally establishes the confidence of the patient in his physician, a vital factor in successful therapy.

If medicine abandons its historic support of the principle of free choice, it can expect increasing third party interference in decisions on predominantly professional matters.

The number of third parties is growing; the number of persons they serve is increasing. Unless medicine soon contains the influence of third parties on medical practice, it can expect the worst.

However, I believe that we can prevent the extension of third party influence by adhering uncompromisingly to the basic principle of free choice, by rendering competent medical care at a cost which patients can afford, by assuring the public of the competence of licensed physicians, and by policing our ranks to eliminate professional incompetence or economic abuses.

These must be self-imposed responsibilities that must be discharged vigorously now and in the future or medicine may well find itself completely subservient to the third party!

GUNNAR GUNDERSEN, M.D.
La Crosse, Wis.

MEDICAL NEWS

ARKANSAS

New Clinical Research Wing.—The University of Arkansas Medical Center, Little Rock, has been awarded a $1,088,000 grant by the U. S. Public Health Service to help finance construction of a nine-story clinical research wing. The money will be matched dollar-for-dollar by private funds being raised within the state. The Medical Center now is composed of an eight-story hospital and a nine-story educational wing. A 10-story student dormitory and adjoining student union building are under construction. The federal grant for the research wing was one of four in excess of one million dollars in the USPHS announcement of a total of $30,000,000 awarded to medical institutions throughout the nation. The money was appropriated by Congress to expand health research facilities.

Medicine's "Festival of Faith" in Tyronza.—Sponsored by the First Councillor District of the Arkansas Medical Society, American Medicine's "Festival of Faith" will be held Oct. 2 at Tyronza, 28 miles northwest of Memphis. A medical educational symposium of students, teachers, and hospital staffs will be conducted from 11 a. m. to 12:30 p. m., moderated by Dr. Willis E. Brown, head, department of gynecology and obstetrics, University of Arkansas School of Medicine, Little Rock. A section of the symposium will be the quiz class in which seven medical school deans will be quizzed on the topic "The Why in Medicine and Medical Schools." General chairman for the afternoon session will be Dr. David B. Allman, Atlantic City, N. J., immediate past-president of the A. M. A. Speakers will include Dr. Austin Smith, editor of THE JOURNAL; Dr. George M. Fister, Ogden, Utah; Mrs. E. Arthur Underwood, Vancouver, Wash., president of the Women's Auxiliary of the A. M. A.; and Dr. Louis M. Orr, Orlando, Fla., president-elect of the A. M. A. Scientific papers will include the following:

Smoking and Its Relation to Cancer of Lung, Dr. Alton Ochsner, New Orleans, La.

The Philosophy of Human Nature As Related to Surgery, Dr. Philip Thorek, Chicago, Ill.

Pathology is the Foundation of Medicine, Dr. Mervin H. Grossman, Dallas, Texas.

One Man's Hope in Treatment of Cancer, Dr. Fred E. Woodson, Tulsa, Okla.

The Governor's Committee on Employment of the Physically Handicapped will convene at 3 p. m. For information write Dr. Lowry H. McDaniel, Chairman, Program Committee, American Medicine's Festival of Faith, Tyronza, Ark.

CALIFORNIA

Dr. Brem Appointed Chairman of Department of Medicine.—Promotion of Dr. Thomas H. Brem to be chairman of the department of medicine in the University of Southern California School of Medicine, Los Angeles, has been announced by Dr. Clayton G. Loosli, dean, following the retirement of Dr. Merritt P. Starr, head of the department from 1948 to 1955. Drs. Brem and Starr have shared the chairmanship the past three years, Dr. Brem being in charge of teaching and Dr. Starr in charge of research. Henceforth, Dr. Brem will be responsible for both fields. Until Dr. Loosli arrived July 1 from the University of Chicago to become dean, Dr. Brem also has served as chairman of the interim administrative committee of the Medical School following the resignation of Dr. Gordon Goodhart as dean in 1956. He is a member of the American Board of Internal Medicine.

Committees to Select Medical and Surgical Executives.—Two special committees have been named to select new men for the positions held by Dr. David A. Rytand and Dr. Victor Richards on the Stanford Medical School faculty, Dean Robert H. Alway has announced. Dr. Rytand has asked to be relieved of his executive duties while continuing as professor of medicine. Dr. Richards resigned as executive of the surgery department, effective Sept. 1. On the committee in search of a medical department executive are Associate Dean Lowell Rants, Drs. Alvin J. Cox Jr., Frank L. A. Gerbode, Avram S. Goldstein, Arthur Kornberg, Dwight L. Wilbur, and Albert M. Snell. On the surgery executive committee are Drs. Gerbode, William P. Creger, Roy B. Cohn, Sidney Raffel, and Henry S. Kaplan. Dr. Alway has asked both committees to report on candidates as soon as possible. The new Stanford Medical School opens on the campus Sept. 1 next year.

General Practice Meeting in San Francisco.—The California Academy of General Practice will hold its 10th scientific assembly Oct. 5-8 in the Masonic Temple, San Francisco. Dr. Ethan A. Brown, Boston, will present the Stanley R. Truman Lecture, "Reactions to Antibiotics, Especially Penicillin,"

Physicians are invited to send to this department items of news of general interest, for example, those relating to society activities, new hospitals, education, and public health. Programs should be received at least three weeks before the date of meeting.

and Dr. Ralph C. Benson, Portland, Ore., will give the Ivan C. Heron Lecture, "Third Trimester Obstetrical Problem." Presentations by other out-of-state speakers are:

Teenage Sex Education, Dr. Robert N. Rutherford, Seattle.
Psychotherapy in the GP's Office, Dr. C. H. Hardin Branch, Salt Lake City.
Is It Angina?, Dr. William H. Gordon, Lubbock, Texas.
Use and Abuse of Diuretics, Dr. Gordon.
"If I Had An Ulcer . . .", Dr. Philip Thorek, Chicago.

Technical exhibits and the annual informal party are planned. For information write the California Academy of General Practice, 461 Market St., San Francisco.

GEORGIA

Clinical Society Meeting.—The first annual meeting of the Grady Hospital Clinical Society, an association composed of former members of the intern and resident staff of the Grady Memorial Hospital, will be held Oct. 20 at the Grady Memorial Hospital, Atlanta. Address all inquiries to the Grady Hospital Clinical Society, Room G-610, Grady Memorial Hospital, 80 Butler St., S. E., Atlanta, Ga.

ILLINOIS

Hospital Lecture Series Opens.—The opening lecture in the ninth annual North Shore Hospital Lecture Series on "Emotional Forces in the Family" will be held at the hospital, in Winnetka, Oct. 1, 8:00 p. m. "The development of the Family in the Technical Age" will be discussed by Dr. Joost A. M. Meerloo, of The New York School of Social Research, New York City. The Commission on Education of the American Academy of General Practice has approved these lectures for category II credit. The J. B. Lippincott Company of Philadelphia will publish the entire series as a book. All royalties that accrue have been assigned to the American Psychiatric Association as in previous series. Physicians and allied professional personnel are cordially invited.

Anesthesiologists Meet in Peoria.—On Oct. 4-5 the Illinois Society of Anesthesiologists will meet at the Hotel Pere Marquette, Peoria. The scientific program will include the following:

Preparation of the Diabetic Patient for Surgery, Dr. Lucille A. Sprenger, Peoria.
Pulmonary Resection at Wisconsin General Hospital—15 Years Experience, Dr. Oswald S. Orth, Madison, Wis.
Anesthetic Management of Infants and Children Undergoing Thoracic Operations, Dr. William O. McQuiston, Peoria.

Other participants include Drs. Herbert M. Epstein, Evanston, William K. Stephan, Joliet, and Max S. Sadove, Chicago. Entertainment includes golf and a dinner, Oct. 4. For information write Mr. Clifford A. Baldwin Jr., 432 Jefferson Building, Peoria, Ill., Secretary.

Chicago

Hospital News.—The Michael Reese Hospital Medical Center has announced the appointment of Dr. Sidney Cohen, formerly associate director of laboratories, Beth Israel Hospital, Boston, to head the microbiology department of the center's Research Institute, succeeding Dr. Albert Milzer, who retired.

Tribute to Dr. Rothman.—"In tribute to the research and teaching in dermatology of Dr. Stephen Rothman," professor of medicine and head of the section on dermatology of the School of Medicine of the University of Chicago, the Society for Investigative Dermatology has dedicated the July issue of its journal to him which is limited to scientific reports by former students of Dr. Rothman. Dr. Rothman received his M.D. degree in 1917 from the University of Budapest, and has been at the University of Chicago since 1938. He is chairman of the committee on cosmetics of the American Medical Association, and of the subcommittee on the cutaneous system, of the National Research Council. He has been president of the Society for Investigative Dermatology, which elected him an honorary member in June.

Personal.—The distinguished service award gold medal of the National Medical Association, given each year "for the most distinguished service rendered to the profession on the National level," has been awarded to Dr. Leonidas H. Berry, clinical assistant professor of medicine, University of Illinois College of Medicine, "for his pioneering efforts and success in the Specialty of Diseases of the Stomach, and the 'Berry Plan' of treatment for Drug Addicts."——Martin E. E. Hanke, Ph.D., associate professor of biochemistry, University of Chicago, has been named director of the university's clinical chemistry laboratory. Among the purposes of this appointment is a consolidation of the work in clinical chemistry which is now being done independently in the various clinical departments and hospitals of the university.——Dr. Max Thorek, founder and secretary-general, International College of Surgeons, was decorated as a Commander of the Order of Merit of the Republic of Italy by Giacomo Profili, counsel general of Italy, Sept. 10.

LOUISIANA

Dr. Meleney Goes to Florida.—Dr. Henry E. Meleney, emeritus professor of preventive medicine, New York University College of Medicine, New York City, and research professor of medicine, Louisiana State University, New Orleans, will retire from his present position Sept. 30 and will become assistant health officer of Alachua County, Gainesville, Fla. His special responsibility will be the development of research and personnel training

programs. He will also do teaching at the College of Medicine of the University of Florida, Gainesville.

MICHIGAN

Accidents Among School Children.—Almost half of all deaths among Michigan children of school age are caused by accidents, the Michigan Department of Health has announced. Dr. Goldie B. Corneliuson, director of maternal and child health for the state health department, said that in 1957, accidents claimed 510 lives of school-age children in Michigan, or 47% of the total deaths in that age group. Motor vehicles accounted for the major share of the accidental deaths, causing 294 fatalities, or 58% of the total accidental deaths.

MISSOURI

Lectures for Hospital's Anniversary.—A series of special lectures, sponsored by the clinical departments of Saint Louis University School of Medicine in observance of the 25th anniversary of Firmin Desloge Hospital will continue through November. The department of pediatrics will present its program Oct. 15-16, and an interdepartmental program will be held Nov. 19. Members of the medical profession are invited to attend the lectures and luncheon at Desloge free. The programs have been approved for category I credit by the American Academy of General Practice. Dr. William H. Vogt Jr. is chairman, Firmin Desloge Jubilee Committee.

NEBRASKA

Grant for Training in Rehabilitation.—Creighton University School of Medicine, Omaha, has received the first of five annual grants from the office of Vocational Rehabilitation, Washington, D. C. The grant, to be directed by Dr. Harold N. Neu, professor of medicine and coordinator of the teaching of rehabilitation, will be used "to implement personnel needed to help train medical students and residents in the modern concepts of rehabilitation." Creighton developed an organized teaching program in rehabilitation five years ago. The grant became effective Sept. 1.

NEW YORK

New Health Department in Monroe County.—Establishment of a county health department in Monroe County has been approved by Dr. Herman E. Hilleboe, state health commissioner. Monroe is the 20th county in the state to set up a health department. The new department was expected to begin operating by Sept. 1.

Society News.—At a recent meeting of the Queens Pediatric Society, the following officers were elected: president, Dr. Benjamin Goldsmith, Flushing; vice-president, Dr. Frederick Castrovinci, Jackson Heights; secretary, Dr. Emanuel Fletcher, Flushing; and treasurer, Dr. Elmer E. Amerman, Flushing. The society meets at the Seminole Club, Forest Hills, N. Y., on the second Tuesdays of October, December, February, and April at 7:00 p. m.—The Medical Society of the State of New York has announced the removal of its offices to 750 Third Ave., New York 17; phone, YUkon 6-5757.

Meeting of Physicians in Syracuse.—Dr. John H. Talbott, governor for Western New York, American College of Physicians, will open the annual meeting for that region Oct. 3 at the Syracuse Hotel, Syracuse. Twelve papers are scheduled for the two morning sessions of the one-day meeting. Dr. Howard P. Lewis, Portland, Ore., president-elect of the college, will be guest speaker at luncheon. In the afternoon a panel discussion, "The Present Status of Cardiac Surgery," will be introduced by Dr. Richard H. Lyons, of Syracuse, with Dr. Paul N. Yu, of Rochester, as chairman. A schedule of events for wives and guests is arranged. Registration fee for physicians is $10 and includes luncheon and the social hour at 4 p. m. For reservation and information write to Dr. Henry W. Retan, Syracuse Kemper Bldg., Syracuse 2, N. Y.

Personal.—Dr. Donald F. McDonald, head of the division of urology, University of Washington School of Medicine, Seattle, since 1952, has been appointed professor of urology and chairman of the division at the University of Rochester School of Medicine and Dentistry. Dr. McDonald also will be urologist-in-chief in Strong Memorial Hospital of the Medical Center. He will begin his new duties about Oct. 1 as successor to Dr. Winfield W. Scott, who will become professor of urological surgery emeritus after having served on the medical faculty for 30 years.—Dr. Paul V. Newland, formerly with the Procter & Gamble Co., has been named a staff member of The Norwich Pharmacal Company's medical department in Norwich, Dr. Paul F. MacLeod, department director, has announced.—Dr. William Nussbaum of Kew Gardens was elected to fellowship of the Royal Anthropological Institute of Great Britain and Ireland in May.

Memorial Teaching Day in Binghamton.—The third Samuel E. Cohen Memorial Teaching Day will be held Oct. 1 in the Carlton Hotel, Binghamton, with the theme, "Diagnosis and Therapeutics of Infection." The four speakers, arranged for through the cooperation of the Council Committee on Public Health and Education, Medical Society of the State of New York, and the New York State Department of Health, will present the following:

Principles in the Diagnosis of Infections, Dr. Charles M. Samet, Boston.

The Surgeon and Infection, Dr. Harold A. Zintel, New York City.

Kidney Diseases, Dr. Mitchell I. Rubin, Buffalo.

Newer Concepts in Diagnosis and Treatment of Rheumatoid Arthritis, Dr. Richard H. Freyberg, New York City.

In the evening, a round-table discussion of the afternoon presentations will be held. Postgraduate credit is given to members of the American Academy of General Practice. For information write Mr. Charles Bishara, Executive Secretary, Broome County Medical Society, 42 Front St., Binghamton, N. Y.

New York City

Dr. Thomas to Give Brown Memorial Lecture.—Dr. Lewis Thomas, chairman, department of medicine, New York University College of Medicine, New York City, will give the George Elgie Brown Memorial Lecture on "The Role of Hypersensitivity in Cardiovascular Diseases" Oct. 23 at the 31st annual meeting of the American Heart Association at San Francisco Oct. 24-26. This lecture was established in memory of Dr. George Elgie Brown formerly head of a section of medicine in the Mayo Clinic, Rochester, Minn.

Personal.—Dr. I. Newton Kugelmass, consultant to the departments of health and hospitals, New York City, addressed the department of pediatrics, University of Tokyo, Aug. 11 on the "Mechanism and Management of Hemorrhagic Disorders in Infants and Children."—Dr. Charles A. Carton has been appointed chief of the division of neurosurgery of Montefiore Hospital. He also will serve as associate clinical professor of surgery at the Albert Einstein College of Medicine.—Dr. David Grob, associate professor of medicine at Johns Hopkins University School of Medicine, Baltimore, has been appointed professor of medicine at the State University of New York Downstate Medical Center and full-time director of medical services at Maimonides Hospital of Brooklyn.—Dr. Brewster S. Miller, lecturer in neoplastic diseases at New York Medical College, has been appointed medical director of United Cerebral Palsy Associations, Inc., and research director of the United Cerebral Palsy Research and Educational Foundation, Inc.

Symposium on Diabetes.—"The Brain and Diabetes Mellitus" will be the subject of an all-day symposium sponsored by the Clinical Society of the New York Diabetes Association, to be held Oct. 10 at Hunter College Playhouse Auditorium, New York City. The program lists the following speakers:

Metabolism of the Brain and Its Relation to Diabetes Mellitus, Dr. Seymour S. Kety, Philadelphia.
Pathological Effects of Hypoglycemia, Dr. Harry M. Zimmerman, New York City.
Hypothalamic Control of the Anterior Hypophysis and Its Metabolic Implications, Dr. Roger Guillemin, Houston, Texas.
Role of the Highest Integrative Functions of the Central Nervous System in Disease, Dr. Harold G. Wolff, New York City.
Clinical Experience with Oral Hypoglycemic Agents, Dr. Garfield G. Duncan, Philadelphia.
Surgery of Segmental Vascular Disease, Dr. Ernest S. Crawford, Houston, Texas.

A panel discussion, "The Role of Environment and Personality in the Management of the Difficult Patient with Diabetes Millitus," will open the afternoon session. The symposium is sponsored by grants-in-aid from Charles Fischer and Company, Inc. Physicians, medical students, and professional personnel are invited. There is no registration fee but advanced registration is required. For information write the New York Diabetes Association, Inc., 104 E. 40th St., New York 16.

NORTH CAROLINA

Expand Duke's Allergy Training Program.—The National Institute of Allergy and Infectious Diseases, U. S. Public Health Service, has awarded Duke University Medical Center a $127,000 graduate training grant toward support of the expanded allergy program for five years. Primarily, the expansion consists of increasing the program to include research and clinical work in the allied areas of genetics, immunology, chest disease, and physiology. The work also will involve studies of the basic problems of tissue transplantation and immunological aspects of tumor research. Dr. Herbert O. Sieker, assistant professor of medicine at Duke, is director of the program. Dr. Sieker explained that the clinical allergy service at Duke Hospital is being expanded to offer diagnosis and treatment of all kinds of allergic disorders.

PENNSYLVANIA

Annual State Meeting in Philadelphia.—The Medical Society of the State of Pennsylvania will hold its 108th annual session at the Bellevue-Stratford Hotel, Philadelphia, Oct. 12-17. The general sessions will be presented as panel discussions under the following titles and moderators:

Hazards of Antibiotic Therapy, Dr. Abraham I. Braude, Pittsburgh.
Trends in Medical Care, Dr. Wendell B. Gordon, Pittsburgh.
Steroids—Uses and Abuses, Dr. Thaddeus S. Danowski, Pittsburgh.
Reduction of Mortality and Morbidity in Automobile Accidents—The Physicians' Responsibility, Dr. Constantine P. Faller, Harrisburg.
The Chronically Tired Patient—An Important Complaint, Dr. Allen W. Cowley, Harrisburg.
Special Consideration in the Care of Patients Having Malignant Disease, Dr. Charles S. Cameron, Philadelphia.

A clinicophysiologic conference, "Neonatal Crises . . . ," will be moderated by Dr. Lewis A. Barness, Philadelphia. The 11th annual state dinner will be held the evening of Oct. 14. Alumni dinners and the president's reception are arranged for Oct. 15. For information write the Medical Society of the State of Pennsylvania, 230 State St., Harrisburg, Pa.

Philadelphia

Municipal Public Health Appointments.—The Philadelphia Department of Public Health has announced the appointment of three physicians each of whom holds the degree of master of public health. Named chief of the department's Maternal and Child Health Section was Dr. Donald A. Cornely, who had been chief of medical education at Philadelphia General Hospital. Dr. Harriett C. Jones was appointed to the District Health Operations unit, which has the responsibility for program planning and execution in the city's 10 health districts and health centers. Dr. Thomas W. Georges Jr., will be assistant director of the health program in Philadelphia's Health District 1. Dr. James P. Dixon, health commissioner, said that additional positions are available including those of director of the Disease Control Division, chief of the Tuberculosis Control Section, and directors of health district programs.

TENNESSEE

Mental Hospital for Medical Center.—The Medical Center in Memphis, in which the University of Tennessee shares prominently, is soon to have a state hospital for the mentally ill. The master plan for a six-million-dollar mental health center will use the entire block across from LeBonheur Hospital. The land is now being cleared and by October work will start on the 3¼-million-dollar 200-bed hospital. Training and research faculties now handled in present university facilities and Gailor Psychiatric hospital will be transferred to the mental health center as the buildings are completed. The fields of training will include psychiatric residents, clinical psychology, social work, nursing psychiatry, and occupational and recreational therapy.

TEXAS

Dr. DeBakey Awarded Alvarenga Prize.—On July 14 the College of Physicians of Philadelphia awarded the Alvarenga Prize for 1958 to Dr. Michael E. DeBakey, professor of surgery, Baylor University College of Medicine, Houston, "for his outstanding work in the surgical treatment of diseases of blood vessels." The Alvarenga Prize was established by the will of Pedro Francisco DaCosta Alvarenga, of Lisbon, Portugal, an associate fellow of the College of Physicians of Philadelphia, to be awarded annually by the college on the anniversary of the death of the testator, July 14, 1883.

Annual Award for Research in Psoriasis.—The department of dermatology, Baylor University College of Medicine, Houston, has announced an International Memorial Award for Psoriasis Research, established as a 10-year program by Carol and Henry J. N. Taub in honor of their grandparents. An annual award of $1,000 for research on psoriasis, it is designated "for the individual or group who has done the most out-standing investigative work in this field." Results of the research must have been presented before a dermatological medical society or published in a recognized medical journal. The name of any applicant for the award, together with supporting data, should be submitted for consideration by Dec. 1. The recipient will be determined by a committee composed of Drs. Marcus R. Caro, Edward P. Cawley, Arthur C. Curtin, Eugene M. Farber, John M. Knox, Aaron B. Lerner, and Carl T. Nelson. Address all communications to Dr. John M. Knox, Department of Dermatology, Baylor University College of Medicine, Houston 25, Texas.

VERMONT

Dr. Bland to Study in England.—Dr. John H. Bland, associate professor of medicine, University of Vermont College of Medicine, and director of the Arthritis Clinics at the Mary Fletcher and DeGoesbriand Memorial hospitals, in Burlington, has left on a one-year leave of absence for Manchester, England, where he will be associated with Prof. Jonas H. Kellgren, director of the Rheumatism Research Center at the University of Manchester, where each year scientists are invited to work and study. Dr. Bland, one of two M.D.'s invited this year, will work in the area of connective tissue biochemistry. He plans to visit several European universities to discuss connective tissue investigation and plans to make a comparative study of medical education methods in England, Europe, and the United States. Dr. Bland's leave is under the auspices of the Nuffield Foundation in England, the Commonwealth Fund of New York, the New England Chapter of the Arthritis and Rheumatism Foundation, and the National Institutes of Health. During Dr. Bland's leave, the two active clinics of the DeGoesbriand Memorial and Mary Fletcher Hospitals will be under the direction of Dr. Winston M. Eddy, of Burlington.

WISCONSIN

Dr. Engstrom Appointed Department Chairman.—Dr. William W. Engstrom, associate professor of medicine, Marquette University School of Medicine, Milwaukee, has been named the Francis D. Murphy professor and chairman of the department of medicine, effective Aug. 15. Dr. Engstrom assumes the post held by Dr. Francis D. Murphy, who will remain a professor in the department and active in the teaching program of the medical school. Dr. Engstrom has also been appointed director of medicine of Milwaukee County Hospital, a post held by Dr. Murphy for 33 years.

GENERAL

Congress on Safety in Chicago.—The 46th National Safety Congress and Exposition will be held Oct. 20-24, with activities at the Conrad Hilton, Sheraton–Blackstone, Pick–Congress, Hamilton, La Salle, and Morrison Hotels, Chicago. The 13th annual Federal Safety Conference, sponsored by the Federal Safety Council, will be held Oct. 20-21. Over 45 section meetings will be held for discussion of safety in industry, farming, mining, transportation, and commerce. A program of safety films and exhibits is arranged. The American Society of Safety Engineers will meet Oct. 21, with an annual chapter achievement awards luncheon at 12:15 p. m. Entertainment for the congress includes the banquet Oct. 22, 6:30 p. m., at the Conrad Hilton Hotel. Registration fee is $5. For information write the National Safety Council, 425 N. Michigan Ave., Chicago.

Meeting on Surgery of Trauma.—The American Association for the Surgery of Trauma will hold its 18th annual session Oct. 2-4 at the Drake Hotel, Chicago. The presidential address will be given the afternoon of Oct. 3 by Dr. William L. Estes Jr., Bethlehem, Pa. Over 40 papers are scheduled for presentation including the following by Canadian authors: "Traumatic Diplopia," Dr. Arthur L. Murphy, Halifax, Nova Scotia, and "First Aid Equipment for Traffic Accidents," Dr. John C. Dickison, Montreal. A symposium on "The Impartial Medical Testimony Plan" will be moderated by Dr. William E. Mishler, Cleveland. Dr. Percival Bailey, professor of neurology and neurological surgery, University of Illinois College of Medicine, Chicago, will present "The Seat of the Soul" at the banquet, 8 p. m., Oct. 3. For information write Dr. James K. Stack, 700 N. Michigan Ave., Chicago 11.

Annual Meeting on Clinical Orthopedics.—The 46th annual meeting of the Clinical Orthopaedic Society will be held Oct. 2-4 in Denver and Colorado Springs, under the presidency of Dr. Marcus J. Stewart, Memphis, with headquarters at the Brown Palace Hotel, Denver. The program includes over 40 clinical presentations and the following Denver speakers will present three papers each: Dr. Murray E. Gibbens, Dr. John T. Jacobs Jr., Dr. Mack L. Clayton, and Dr. James S. Miles. Discussion periods will follow each speaker's presentations. Presiding at the clinical sessions will be Drs. Rufus H. Alldredge, New Orleans; Rudolph S. Reich, Cleveland; Gordon C. Whiston, Casper, Wyo.; Charles R. Rountree, Oklahoma City; Clinton L. Compere, Chicago; and Frank O. McGehee, Houston, Texas. Entertainment includes golf, swimming, riding, ice skating, and the annual banquet Oct. 3, 6:30 p. m. For information write Dr. Charles H. Frantz, 1810 Wealthy St., S. E., Grand Rapids, Mich.

Roentgen Ray Society Meeting in Washington, D. C.—The American Roentgen Ray Society will hold its 59th annual meeting Sept. 30-Oct. 3 at the Shoreham Hotel, Washington, D. C. The Caldwell Lecture will be delivered the evening of Sept. 30 by Dr. Leo G. Rigler, president, Radiological Society of North America, on "Functional Roentgen Diagnosis—Anatomical Image—Physiological Interpretation." Of the 39 scheduled papers, the following are by Canadian authors:

Roentgenological Features of Meningeal Fibroblastoma, Dr. Sidney P. Traub, Saskatoon, Saskatchewan.

Tomography in the Radiological Evaluation and Differentiation of Chronic Hypertrophic Emphysema and Asthma, Drs. Robert G. Fraser and David V. Bates, Montreal, Quebec.

Investigation of Effects of Opaque Media on the Lungs with Comparison of Barium Sulphate, Lipiodol and Dionosil, Drs. G. Bernard Skinner, George I. Wortzman, James R. Stuart, and John S. Dunbar, Montreal.

A golf tournament and golf dinner are planned for Sept. 28. President-elect Dr. Barton R. Young is chairman of the committee on arrangements for the scientific program.

Southeastern Physicians Meeting in Biloxi.—The American College of Physicians will hold a southeastern regional meeting (Alabama, Florida, Georgia, South Carolina, and Cuba) Oct. 3-4 at the Buena Vista Hotel, Biloxi, Miss. Of the twenty papers scheduled, the following include guest authors:

Clinical and Physico-Chemical Studies on Macroglobulinemia, Dr. William J. Hammack and Willard R. Starnes, M.S., Birmingham.

Nitroglycerin by Inunction in the Treatment of Angina Pectoris, Dr. James A. Davis, Birmingham.

Preliminary Report on Retrograde Catheterization of the Left Ventricle, Drs. Francisco A. Hernandez, H. R. Cooper, and Herbert Eichert, Miami, Fla.

Myelofibrosis, Drs. Charles C. Corley Jr. and Charles M. Huguley Jr., Atlanta, Ga.

Peripheral Neuropathy in Myxedema, Drs. Lamar E. Crevasse and Robert B. Logue, Atlanta, Ga.

Coronary Disease in the Negroes of Haiti and the United States, Drs. Dale Groom, Edward E. McKee, Charles Webb, B.S., and Faye W. Grant, Ph.D., Charleston, S.C., and Dr. Vergniaud Pean, Port-au-Prince.

At the dinner session Oct. 3, Dr. Dwight L. Wilbur, San Francisco, president, American College of Physicians, will present an address. For information write Dr. Duward O. Wright, 2930 N. 16th St., Birmingham 2, Ala., Governor for Alabama.

Annual Meeting of Pediatricians.—The 27th annual meeting of the American Academy of Pediatrics will be held Oct. 18-23 at the Palmer House, Chi-

cago. Two-day seminars will be held Oct. 18-19, and half-day round-tables will run concurrently with the general sessions. The Borden award presentation will be given Oct. 20 by Dr. Charles D. May, New York City, on "Protein Allowance in Infant Nutrition." Five symposiums are planned, with the following titles and chairmen:

Regulation of Carbohydrate Metabolism, Dr. Rachmiel Levine, Chicago.

Radioactive Isotopes in Pediatric Medicine, Dr. Lee E. Farr, Upton, N. Y.

Cystic Fibrosis of the Pancreas, Dr. May.

Office Evaluation of Intelligence and the Special Senses, Dr. Harry Bakwin, New York City.

Recent Developments in Control of Infectious Diseases, Dr. Edward C. Curnen Jr., Chapel Hill, N. C.

A panel discussion on "The Pediatrician's Responsibility in Mental Health Counseling" is planned for Oct. 21, with Dr. Sherman Little, Buffalo, N. Y., as chairman. A banquet, a program of ladies' entertainment, and alumni meetings are arranged. For information write Dr. Einor H. Christopherson, P. O. Box No. 1116, Evanston, Ill., Executive Secretary.

Plastic Surgeons Meeting in Chicago.—The 27th annual meeting of the American Society of Plastic and Reconstructive Surgery will be held Oct. 12-17, with headquarters at the Drake Hotel, Chicago. Foreign participants will include Drs. Fernando Ortiz-Monasterio and R. Serrano, Mexico City, who will present "Cephalometric Measurements on Adult Patients with Nonoperated Cleft Palates," and Drs. Hamilton A. Baxter and Marcy A. Goldstein, Montreal, Canada, who will give "Duration of Survival of Human Fetal Grafts." The program includes four symposiums and the following papers with invited guest authors:

Place of Radiation Therapy in Treatment of Advanced Carcinoma of Lower Lip, Dr. Isadore Lampe, Ann Arbor, Mich.

Vascular Reinforcement of Pedicled Tissues Using Histamine Iontophoresis, Drs. Richard B. Stark and Clayton R. De Haan, New York City.

Homotransplantation of Thyroid and Parathyroid Glands by Vascular Anastomoses, Drs. Herbert Conway and James W. Smith, New York City.

Skin Grafting Procedures in Injuries of the Hand, Dr. Joseph L. Posch, Detroit.

Reconstruction of the Penis, Drs. Jerome Gelb, Maxwell Malament, and Stephen R. Loverme, Newark, N. J.

Exhibits are planned, and entertainment includes the society dinner Oct. 13, 7 p. m., and the president's banquet, Oct. 16, 6 p. m., at which Mr. Ralph G. Newman will talk on Abraham Lincoln and Dr. Wallace H. Steffensen, president of the society, will speak. For information write Dr. Kenneth L. Pickrell, Duke Hospital, Durham, N. C.

Prevalence of Poliomyelitis.—According to the National Office of Vital Statistics, the following number of reported cases of poliomyelitis occurred in the United States, its territories and possessions in the weeks ended as indicated:

Area	Aug. 30, 1958		Aug. 31, 1957
	Paralytic Type	Total Cases	Total
New England States			
Maine	..	..	..
New Hampshire	..	..	1
Vermont	..	..	1
Massachusetts	..	4	..
Rhode Island	..	..	..
Connecticut	..	2	6
Middle Atlantic States			
New York	4	13	19
New Jersey	10	23	8
Pennsylvania	3	4	4
East North Central States			
Ohio	8	22	16
Indiana	5	10	6
Illinois	5	15	31
Michigan	25	69	47
Wisconsin	..	6	20
West North Central States			
Minnesota	2	2	1
Iowa	2	2	2
Missouri	7	16	8
North Dakota	1	1	3
South Dakota	..	..	2
Nebraska	..	1	3
Kansas	..	..	1
South Atlantic States			
Delaware	..	..	..
Maryland	..	1	..
District of Columbia	..	..	6
Virginia	5	6	3
West Virginia	10	13	2
North Carolina	1	2	6
South Carolina	..	..	1
Georgia	2	3	2
Florida	4	5	1
East South Central States			
Kentucky	1	1	7
Tennessee	1	5	8
Alabama	1	1	..
Mississippi	1	1	1
West South Central States			
Arkansas	..	..	..
Louisiana	4	5	12
Oklahoma	..	..	2
Texas	17	28	16
Mountain States			
Montana	..	..	2
Idaho	..	..	..
Wyoming	..	..	..
Colorado	..	..	1
New Mexico	..	..	1
Arizona	1	3	1
Utah	..	..	1
Nevada	..	..	..
Pacific States			
Washington	..	..	..
Oregon	3	5	..
California	3	4	20
Territories and Possessions			
Alaska	..	..	..
Hawaii	1	1	..
Puerto Rico	2	2	..
Total	129	283	272

CANADA

Seminar on Blood Banking in Montreal.—A two-day Seminar in Blood Banking and Immunohematology will be held at The Royal Victoria Hospital, Montreal, Quebec, Oct. 16-17. The seminar is designed to demonstrate the newest techniques. The program will be the same on both days. There is no registration fee. Medical personnel interested in attending should communicate with the Post-Graduate Board, Montreal, Royal Victoria Hospital, soon, indicating their choice of dates.

EXAMINATIONS AND LICENSURE

MEDICAL SPECIALTY BOARDS

AMERICAN BOARD OF ANESTHESIOLOGY: *Oral Examination.* San Francisco, Sept. 29-Oct. 3, and Phoenix, April 5-10, 1959. The 1959 written examination will be given in various locations in the United States and Canada, July 17. The final date for filing application for the 1959 written examination is six months prior to the examination. There is no filing deadline for oral examinations. Sec., Dr. Curtiss B. Hickcox, 217 Farmington Ave., Hartford 8, Conn.

AMERICAN BOARD OF DERMATOLOGY: *Written. Several Cities,* June 30. *Oral.* Detroit, Oct. 17-19. Final date for filing all applications is April 1. Sec., Dr. Beatrice Maher Kesten, One Haven Ave., New York 32.

AMERICAN BOARD OF INTERNAL MEDICINE: *Written.* Oct. 20, 1958. *Oral.* Chicago, Oct. 13-16. *1959 Schedule—Written,* Oct. 19. Final date for filing application is May 1. *Oral.* For candidates in the South and Southwest, New Orleans, Feb. 3-6. Final date for filing application is Jan. 1. *Oral.* For candidates in the Midwest. Chicago, April 15-18. Final date for filing application is Jan. 1. *Oral.* For candidates on the West Coast. Final date for filing application is March 1. *Oral.* For candidates on the East Coast, Nov. 6-7, 9-10. Final date for filing application is March 1. *Examination in the Subspecialties. Gastroenterology.* Philadelphia, April 17-18. Final date for filing application is Feb. 1. Sec.-Treas., Dr. William A. Werrell, One West Main St., Madison 3, Wis.

AMERICAN BOARD OF NEUROLOGICAL SURGERY: Examination given twice annually, in the spring and fall. In order to be eligible a candidate must have his application filed at least six months before the examination time. Sec., Dr. Leonard T. Furlow, Washington University School of Medicine, St. Louis 10.

AMERICAN BOARD OF OBSTETRICS AND GYNECOLOGY: Applications for certification, new and reopened, Part I, and requests for re-examination Part II, are now being accepted. All candidates are urged to make such application at the earliest possible date. Deadline date for receipt of application is September 1, 1958. No application can be accepted after that date. It should be noted by prospective candidates that the deadline date in 1959 is August 1. Sec., Dr. Robert L. Faulkner, 2105 Adelbert Road, Cleveland 6.

AMERICAN BOARD OF OPHTHALMOLOGY: *Written,* qualifying test (Part I), January 1959. Final date for filing application was July 1, 1958. *Oral Examinations 1958* (Part II): Chicago, Oct. 6-10. Sec., Dr. Merrill J. King, Box 236, Cape Cottage Branch, Portland, Maine.

AMERICAN BOARD OF ORTHOPAEDIC SURGERY: *Part II.* Chicago, Jan. 21-23, 1959. Deadline for receipt of applications was Aug. 15. Sec., Dr. Sam W. Banks, 116 South Michigan Avenue, Chicago 3.

AMERICAN BOARD OF OTOLARYNGOLOGY: *Oral.* Chicago, Oct. 6-10. Final date for filing application was April 30. Sec., Dr. Dean M. Lierle, University Hospitals, Iowa City.

AMERICAN BOARD OF PATHOLOGY: Chicago, Oct. 30-Nov. 1. Final date for filing application is Sept. 30. Sec., Dr. Edward B. Smith, Indiana University Medical Center, 1100 W. Michigan St., Indianapolis 7.

AMERICAN BOARD OF PEDIATRICS: *Oral.* Chicago, Oct. 24-26 and New York, Dec. 5-7. Sec., Dr. John McK. Mitchell, 6 Cushman Road, Rosemont, Pa.

AMERICAN BOARD OF PLASTIC SURGERY: *Oral and Written.* Chicago, Oct. 9-11. Final date for receipt of case reports was July 1. Corresponding Secretary, Mrs. Estelle E. Hillerich, 4647 Pershing Ave., St. Louis 8.

AMERICAN BOARD OF PREVENTIVE MEDICINE: *Examination in Public Health.* St. Louis, Oct. 24-26. Final date for filing application was Aug. 15. Sec., Dr. Thomas F. Whayne, 3438 Walnut St., Philadelphia 4.

AMERICAN BOARD OF PSYCHIATRY AND NEUROLOGY: New York City, Dec. 15-16; New Orleans, Mar. 16-17. Training credit for full time psychiatric and/or neurologic assignment in unapproved military programs or services between the dates of Jan. 1, 1950 and Jan. 1, 1954 will be terminated on Jan. 1, 1959. Sec., Dr. David A. Boyd, 102-110 Second Ave. S. W., Rochester, Minn.

AMERICAN BOARD OF RADIOLOGY: *Regular Examination.* Washington, D. C., Dec. 8-11. Final date for filing application was July 1. *Special examination in Nuclear Medicine for those diplomates in Radiology or Therapeutic Radiology.* Washington, D. C., Dec. 6. Final date for filing application is Oct. 1. *Special Examination.* Cincinnati, Mar. 16-19, 1959. Final date for filing application is Nov. 1. Candidates completing training June 30, 1959 are not eligible for the Spring 1959 examinations. Sec., Dr. H. Dabney Kerr, Kahler Hotel Bldg., Rochester, Minn.

AMERICAN BOARD OF SURGERY: Written examinations (Part I) will be held at various centers in the United States, Canada, Hawaii, Puerto Rico, and certain military centers abroad on December 3. The date of the Fall examination in *Part I* has been changed from the last Wednesday of October as announced in its current Booklet of Information to December 3, 1958. Thereafter, examinations in Part I will be held once annually, on the first Wednesday of December. The closing date for filing applications will be August 1. *Part II.* Rochester, Minn., Oct. 20-21; Nashville, Tenn., Nov. 17-18; New York City, Dec. 15-16; Houston, Tex., Jan. 12-13; New Haven, Conn., Feb. 9-10; Durham, No. Car., March 9-10; San Francisco, April 13-14; Indianapolis, May 11-12; Columbus, Ohio, May 14-15. Sec., Dr. John B. Flick, 1617 Pennsylvania Blvd., Philadelphia 3.

BOARD OF THORACIC SURGERY: Various centers throughout the United States. *Written.* Spring of 1959. Final date for filing application is December 1. Sec., Dr. Wm. M. Tuttle, 1151 Taylor Avenue, Detroit 2.

AMERICAN BOARD OF UROLOGY: *Written Examination.* Twenty-five cities throughout the country, Dec. 5. The oral will be given in Chicago in February 1959. Sec., Dr. William Niles Wishard, Jr., 30 Westwood Road, Minneapolis 26.

GOVERNMENT SERVICES

AIR FORCE

Medical Symposium in Japan.—The Eighth Medical Symposium to be held at Yamato Air Station in Japan, Oct. 5-8, is expected to be attended by 250 civilian and military physicians from the United States and several foreign countries. The hosts will be the Fifth Air Force and the U. S. Air Force Hospital at Tachikawa. A group from the Air Force Missile Test Center at Patrick Air Force Base, Fla., will present lectures dealing with current development in missile and space vehicle technology. The Wright Air Development Laboratory will present papers on human factors in space flight. The Aero Medical Laboratory will demonstrate some of the latest equipment. Two national consultants to the Air Force will be among the speakers. Invitations to the symposium have been sent to civilian and military personnel in Nationalist China, Cambodia, Korea, Vietnam, Thailand, the Philippines, Burma, Pakistan, Singapore, India, the United Kingdom, Australia, Japan, and Hong Kong. Major Gen. O. K. Niess, PACAF command surgeon, in announcing plans for the symposium stated that one of the chief objectives was to promote cooperation among scientists concerned with aeronautical and medical development and to stimulate medical research among physicians of the United States Air Force and the Asian nations.

VETERANS ADMINISTRATION

Personal.—Dr. Turner Camp, chief medical officer of the Veterans Administration outpatient clinic in Los Angeles, has been named director of clinics in the VA Department of Medicine and Surgery in Washington, D.C., succeeding Dr. Arthur J. Klippen. Dr. Klippen was appointed director of hospitals in the department in Washington, to fill a position that has been vacant for some time.

PUBLIC HEALTH SERVICE

New Program Called COSTEP.—Assignments under the Commissioned Officer Student Training and Extern Program, which is known as COSTEP, are open each year to medical, dental, engineering, science, nursing, and veterinary students who complete their second or third year of professional education on or before July 1 and who are interested in becoming Reserve Officers in the Public Health Service's Commissioned Corps. Students selected are offered commissions in grades equivalent to those held by officers in the armed forces, and they are placed on active duty not to exceed 120 days. Opportunities for either medical or dental internships or active duty on graduation are also available to qualified students.

One hundred thirty-five students from 120 approved four-year professional schools have spent the present summer in U. S. Public Health Service facilities under the PHS year-round training program. While the largest number of students under COSTEP are employed by the PHS during the summer months, the program is open the year-round so that students attending schools operating on the quarter system can apply throughout the year. Its purpose is fourfold: (1) to stimulate the interest of promising students in careers in the Public Health Service, principal health agency of the federal government; (2) to enable students to further their professional knowledge while gainfully employed; (3) to give students an opportunity to increase their understanding in the functions of government and independent public health agencies; and (4) to provide the PHS with competent help during the vacation months.

The assignments under COSTEP, in general, are (1) laboratory assignments in medical research programs at the National Institutes of Health, Bethesda, Md., and the Communicable Disease Center, Atlanta, Ga., (2) clinical clerkships at Public Health Service hospitals and other medical facilities in the United States and Alaska (usually open to students with three years of professional education), and (3) field assignments in public health activities in a number of places throughout the United States.

MISCELLANEOUS

Applications for National Science Foundation Fellowships Due October 15.—The deadline for applications for National Science Foundation Senior Postdoctoral and Science Faculty Fellowships is Oct. 15, 1958. Announcement of awards will be made on Dec. 5, 1958, by the foundation. Awards will be made in medical and biological sciences including anthropology and psychology (excluding clinical); the mathematical, physical, and engineering sciences; and in selected social science fields. Included as well are interdisciplinary fields which overlap two or more scientific disciplines.

Candidates for Senior Postdoctoral Fellowships must be United States citizens who have held the doctoral degree for a minimum of five years or have equivalent education and experience. The Science Faculty Fellowships are directed toward college teachers of science who wish to improve their competence as teachers. These fellowships are open to application by any United States citizen who holds a baccalaureate degree or its equivalent, has demonstrated ability and special aptitude for science teaching and advanced training, and has taught at the collegiate level for a minimum of three years and intends to continue teaching. Application materials may be obtained from the Division of Scientific Personnel and Education, National Science Foundation, Washington 25, D. C.

DEATHS

Abbissinio, Joseph J. Ⓜ Chicago; Regia Universita degli Studi di Roma, Facolta di Medicina e Chirurgia, Italy, 1937; on the staff of St. Francis Hospital in Blue Island, where he died Aug. 8, aged 48, of coronary thrombosis.

Adler, Ludwig Ⓜ New York City; Medizinische Fakultät der Universität, Vienna, Austria, 1901; associated with the Beth Israel and St. Clare's hospitals; died in New Milford, Conn., Aug. 8, aged 82.

Affhauser, Robert Maurice Ⓜ Chicago; Loyola University School of Medicine, Chicago, 1922; veteran of World War II; member of the city board of health; on the staff of the Englewood Hospital; died Aug. 11, aged 62, of coronary occlusion and arteriosclerosis.

Alexander, Robert Mackey, Reading, Pa.; Jefferson Medical College of Philadelphia, 1910; an associate member of the American Medical Association; past-president of the Berks County Medical Society; specialist certified by the American Board of Internal Medicine; veteran of World War I; visiting physician at the Berks County Tuberculosis Sanatorium; consultant in medicine at the Reading Hospital, where he died Aug. 4, aged 74, of cancer of the ampulla of vater.

Baker, Waldo Zimmerly, Youngstown, Ohio; Ohio State University College of Homeopathic Medicine, Columbus, 1918; member of the Ohio State Medical Association; county jail physician; associated with Youngstown and St. Elizabeth's hospitals; died in St. Mary's Hospital, Rochester, Minn., Aug. 5, aged 67, of cancer of the lung.

Bliss, Howard Clifford, Vestaburg, Pa.; University of Pittsburgh School of Medicine, 1909; past-president of the Rotary Club of Fredericktown; on the courtesy staff of the Brownsville (Pa.) Hospital; died in Uniontown, Pa., July 28, aged 75, of cerebral thrombosis and cerebral arteriosclerosis.

Brager, Louis R., Forest Hills, N. Y.; Long Island College Hospital, Brooklyn, 1912; died in the Park East Hospital, New York City, Aug. 3, aged 72, of myocardial infarction.

Brennan, Alfred Theodore Vincent Jr., Tenafly, N. J.; Columbia University College of Physicians and Surgeons, New York City, 1930; consultant in the department of dermatology at the Holy Name Hospital in Teaneck and for many years associated with the Englewood (N. J.) Hospital, where he died July 31, aged 53, of carcinoma of the tongue.

Ⓜ Indicates Member of the American Medical Association.

Brown, Andrew Dobbie Ⓜ Central City, Neb.; University of Nebraska College of Medicine, Omaha, 1912; died July 30, aged 72.

Brown, Rolla Oscar Ⓜ Kailua, Hawaii; born in Pittsburgh May 7, 1895; University of Pennsylvania School of Medicine, Philadelphia, 1920; specialist certified by the American Board of Urology; member of the American Urological Association; fellow of the American College of Surgeons; fellow in surgery at the Mayo Foundation in Rochester, Minn., from 1922 to 1924; served as a consultant in urology to the Leahi Home and a member of the urologic service of Queen's Hospital in Honolulu, formerly chairman of the Hawaiian Territorial Medical Examiners and secretary of the Hawaii Territorial Medical Association; died at the Good Samaritan Hospital in Los Angeles July 24, aged 63, of cancer of the lung.

Cervone, Louisa Santoro, Youngstown, Ohio; University of Wooster Medical Department, Cleveland, 1900; died in the Woodside Receiving Hospital July 31, aged 80, of arteriosclerosis.

Christensen, Walter Ⓜ North Hollywood, Calif.; Minneapolis College of Physicians and Surgeons, medical department of Hamline University, 1904; died July 21, aged 79, of cerebral thrombosis.

Conrad, Robert Waite Ⓜ St. Joseph, Mo.; George Washington University School of Medicine, Washington, 1943; certified by the National Board of Medical Examiners; veteran of World War II and was decorated for bravery; on the staff of the Missouri Methodist Hospital; died in St. Joseph's Hospital July 27, aged 40, of acute hemorrhagic pancreatitis.

Cook, Elbert Clancy, Bradenton, Fla.; Kentucky School of Medicine, Louisville, 1906; member of the Florida Medical Association; died June 5, aged 80, of a heart attack.

Corbin, Robert Adwood, Hammond, La.; Tulane University School of Medicine, New Orleans, 1914; specialist certified by the American Board of Otolaryngology; veteran of World War I; formerly on the staff of the Touro Infirmary in New Orleans; died in Fort Walton Beach, Fla., July 21, aged 66.

Critchfield, Otis D., West Unity, Ohio; the Hahnemann Medical College and Hospital, Chicago, 1910; veteran of World War I; died in Stryker May 25, aged 75.

Curry, Dalferes Pennington Ⓜ Columbia, S. C.; Kentucky University Medical Department, Louisville, 1903; member of the Medical Association of the Isthmian Canal Zone, of which he was formerly vice-president; served as assistant chief health officer of the Panama Canal Zone; died in the Columbia Hospital July 23, aged 79, of bronchopneumonia and coronary thrombosis.

Danforth, James Chester Ⓜ Grosse Pointe Woods, Mich.; University of Michigan Homeopathic Medical School, Ann Arbor, 1915; on the staffs of the Holy Cross, Grace, and Evangelical Deaconess hospitals in Detroit; died in the Cottage Hospital July 31, aged 70, of cerebral thrombosis.

Dickinson, Almer Edwin, Los Gatos, Calif.; the Hahnemann Medical College and Hospital, Chicago, 1897; died May 20, aged 85.

Dodd, John Edward Ⓜ Framingham, Mass.; Tufts College Medical School, Boston, 1910; fellow of the American College of Surgeons; a member of the board of health for many years; on the staff of the Framingham Union Hospital; died July 25, aged 71, of pulmonary embolism.

Fessman, John William Ⓜ Runnemede, N. J.; Hahnemann Medical College and Hospital of Philadelphia, 1928; veteran of World War II; a director of the Runnemede branch of the Camden Trust Company; chairman of the board of the Camden County Hospital for Chest Diseases, Lakeland; associated with the West Jersey Hospital in Camden, where he died July 28, aged 54, of acute coronary occlusion.

Fett, Bennie John Ⓜ Port Arthur, Texas; University of Tennessee College of Medicine, Memphis, 1932; member and past-president of the staff of St. Mary's Hospital, where he died July 31, aged 50, of acute monocytic leukemia.

Fillmore, Hartson Dustin, Wichita Falls, Texas; University of Tennessee Medical Department, Nashville, 1901; veteran of World War I and the Spanish–American War; died July 30, aged 84, of carcinoma of the lung.

Fisch, Benjamin Ⓜ Brooklyn; Deutsche Universität Medizinische Fakultät, Prague, Czechoslovakia, 1924; died in the Maimonides Hospital July 20, aged 61, of a cerebral vascular accident and arteriosclerosis.

Flower, Morris Aaron Ⓜ Newark, N. J.; Medico-Chirurgical College of Philadelphia, 1911; member of the American Academy of General Practice; on the courtesy staff of Beth Israel Hospital, where he died Aug. 1, aged 71, of cerebral hemorrhage and arteriosclerosis.

Forkin, William Patrick, Chilton, Wis.; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1903; at one time on the staff of the Jacksonville (Ill.) State Hospital; died in the Alexian Brothers Home in Oshkosh July 28, aged 82, of bronchopneumonia chronic purulent bronchitis, and bronchiectasis.

Gibbens, Howard Clinton, Salem, N. J.; Medico-Chirurgical College of Philadelphia, 1903; for many years medical missionary in Burma; died in the Salem County Memorial Hospital July 20, aged 86.

Glassberg, Irving Jeffery Ⓜ Minneapolis; University of Minnesota Medical School, Minneapolis, 1935; specialist certified by the American Board of Urology; member of the American Urological Association; fellow of the American College of Surgeons; at one time on the faculty of Louisiana State University School of Medicine in New Orleans, where he was on staff of the Touro Infirmary; on the faculty of his alma mater; veteran of World War II; died in Mount Sinai Hospital July 28, aged 51.

Gordon, Edward Johnston, Newburgh, N. Y.; Bellevue Hospital Medical College, New York City, 1898; veteran of World War I; served as rating specialist at the Veterans Administration Hospital in Lyons, N. J., and Newark, N. J.; died July 25, aged 83, of arteriosclerotic heart disease and pulmonary emphysema.

Graham, William Alex, Powell, Wyo.; Keokuk (Ia.) Medical College, 1898; died in the War Memorial Hospital June 26, aged 87, of arteriosclerosis.

Halabi, Nour Eddine Ⓜ Bellefonte, Del.; American University of Beirut School of Medicine, Lebanon, 1947; interned at the Alexandria Hospital in Alexandria, Va., where he served a residency; formerly a resident at the Delaware Hospital in Wilmington, Wilmington (Del.) General Hospital, and the Temple University Hospital in Philadelphia; for two years served in the U. S. Army Reserve; died July 24, aged 35.

Haley, Marcus Delafayette Ⓜ Stearns, Ky.; Vanderbilt University School of Medicine, Nashville, Tenn., 1926; on the staff of the Somerset City (Ky.) Hospital; died in St. Joseph's Hospital, Lexington, July 25, aged 63, of cancer of the lung.

Hall, Huger Tudor Ⓜ Aiken, S. C.; Medical College of South Carolina, Charleston, 1934; vice-chief of staff, Aiken County Hospital, where he died July 25, aged 50, of bronchogenic cancer.

Hayward, Eugene Henderson, Baltimore; Baltimore Medical College, 1901; fellow of the American College of Surgeons; an associate member of the American Medical Association; past-president of the Baltimore City Medical Society; veteran of

World War I; associated with Mercy, University, Church Home, Bon Secours, St. Agnes, Maryland General, Provident, and Union Memorial hospitals, and St. Joseph's Hospital, where he died Aug. 5, aged 80, of congestive heart disease and aneurysm of the abdominal aorta.

Heath, Louanna, Maplewood, N. J.; Woman's Medical College of Pennsylvania, Philadelphia, 1903; died in Vineyard Haven, Mass., Aug. 5, aged 78, of acute myocardial infarct.

Hicks, Harvard Raymond, Doylestown, Pa.; University of Pennsylvania School of Medicine, Philadelphia, 1923; veteran of World War II; served as medical director of the Neshaminy Manor Home; affiliated with Presbyterian Hospital in Philadelphia, Abington (Pa.) Memorial Hospital, and the Doylestown Hospital, where he died July 29, aged 61, of coronary sclerosis and peripheral vascular disease.

Holton, Thomas Jefferson, Charlotte, N. C.; Atlanta School of Medicine, 1909; died in Columbia, S. C., July 26, aged 77.

House, Lewis Clinton, El Centro, Calif.; University of Colorado School of Medicine, Denver, 1914; served as president of the Imperial County Medical Society; for many years county health officer; fellow of the American College of Surgeons; on the staff of the Imperial County Hospital; a director of the El Centro Branch, Bank of America; died July 29, aged 75, of terminal pneumonia and uremia.

Hyder, Herman Pettibone ⊗ Bentonville, Ohio; University of Arkansas School of Medicine, Little Rock, 1917; died July 23, aged 73.

Joyce, Reid Petree ⊗ Xenia, Ohio; University of Pennsylvania School of Medicine, Philadelphia, 1932; specialist certified by the American Board of Surgery; fellow of the American College of Surgeons; associated with the Greene Memorial Hospital, where he died July 16, aged 50, of coronary thrombosis.

Killoran, Vincent Ambrose ⊗ Fort Lauderdale, Fla.; University of Toronto Faculty of Medicine, Toronto, Ontario, Canada, 1927; died in Hawaii July 26, aged 58.

Kline, Ralph Glenn ⊗ Hoopeston, Ill.; University of Illinois College of Medicine, Chicago, 1916; served on the faculty of his alma mater; a surgeon for the Chicago and Eastern Illinois Railroad; died in the Lakeview Hospital, Danville, July 28, aged 70.

Long, Samuel Clark, Philadelphia; Medico-Chirurgical College of Philadelphia, 1912; an associate member of the American Medical Association; for many years medical director of the Atlantic Refining Company; on the staffs of the St. Agnes and Methodist hospitals; died Aug. 3, aged 73, of cerebral thrombosis and arteriosclerosis.

Lusk, Hamilton Neal ⊗ Temple, Texas; Baylor University College of Medicine, Dallas, 1905; served as mayor; died in the Scott and White Hospital July 30, aged 81, of leukemia.

Mathis, William Harris, North Augusta, S. C.; University of Georgia Medical Department, Augusta, 1917; veteran of World War I; died in Augusta, Ga., July 28, aged 68.

McCord, Arthur Nelson ⊗ Streator, Ill.; Chicago College of Medicine and Surgery, 1908; also a pharmacist; veteran of the Spanish-American and World War I; on the staff of St. Mary's Hospital; died July 24, aged 88, of rheumatoid arthritis.

Mellin, L. Robert ⊗ Chicago; Bennett Medical College, Chicago, 1914; served as a member of the board of education; veteran of World War I; associated with Alexian and Columbus Memorial hospitals; died in the Albert Merritt Billings Hospital Aug. 6, aged 65, of bronchogenic carcinoma.

Moore, M. Elizabeth, Danbury, N. C.; Woman's Medical College of Pennsylvania, Philadelphia, 1928; county health officer; past-president of the staff of the Stokes-Reynolds Memorial Hospital, where she died July 27, aged 57, of cancer of the right ovary with metastases.

Morris, James Benjamin ⊗ New Bedford, Mass.; College of Physicians and Surgeons, Boston, 1919; veteran of World War I; physician for the board of public welfare; died July 26, aged 63.

Morris, J. F., Harlingen, Texas (licensed in Arkansas in 1903); died July 8, aged 92, of cancer of the mouth.

Munch, Clarence J., Culbertson, Mont.; Jenner Medical College, Chicago, 1915; died July 18, aged 67, of myocardial infarction.

Nickel, Allen Arthur Clarence ⊗ Bluffton, Ind.; Rush Medical College, Chicago, 1924; also an ordained minister; specialist certified by the American Board of Internal Medicine; member of the American College of Chest Physicians and the American Society of Clinical Pathology; fellow of the American College of Physicians; for two years president of the Wells County Medical Society; a partner in the Caylor Nickel Clinic; chief of the department of internal medicine, Clinic Hospital, where he died July 31, aged 63, of pulmonary embolism.

O'Connor, Ralph Edward, Buffalo; University of Buffalo School of Medicine, 1935; member of the Medical Society of the State of New York; associated with the Lafayette General Hospital and

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Emergency Hospital (of the Sisters of Charity) died in the Buffalo General Hospital July 25, aged 59.

O'Keefe, Edward F., Howard, R. I.; Georgetown University School of Medicine, Washington, D. C., 1937; senior physician at the State Infirmary; died July 28, aged 47, of a cerebrovascular accident and cirrhosis of the liver.

Potts, Frank Tuthill ⊗ Lacon, Ill.; Rush Medical College, Chicago, 1904; died in the Decatur and Macon County Hospital in Decatur, July 29, aged 82.

Purviance, Walter ⊗ Pampa, Texas; Keokuk (Ia.) Medical College, College of Physicians and Surgeons, 1902; also a druggist; veteran of World War I; served as mayor; died in Evergreen, Colo., July 24, aged 78.

Rogers, Asa Holt, Philadelphia; Jefferson Medical College of Philadelphia, 1893; died July 30, aged 87, of arteriosclerosis.

Rutledge, Ralph Leyda Sr., ⊗ Alliance, Ohio; University of Pittsburgh School of Medicine, 1916; member of the American Fracture Association and the American Academy of General Practice; past-president of the Ohio State Medical Association and the Stark County Medical Society; veteran of World War I; on the staff of the Alliance City Hospital; died in the Woman's Christian Association Hospital in Jamestown, N. Y., July 23, aged 65, of acute myocardial infarction.

Saferstein, T. Harry ⊗ St. Joseph, Mo.; University of Kansas School of Medicine, Kansas City, Kan., 1930; veteran of World War II; associated with Missouri Methodist and St. Joseph's hospitals; died July 28, aged 52, of coronary occlusion.

Shane, Robert Shoemaker ⊗ Pilot Mound, Iowa; State University of Iowa College of Medicine, Iowa City, 1912; served during World War I; veteran of World War II and served as state selective service medical director; died in Boone County Hospital in Boone July 30, aged 72, of infection and massive liver abscess.

Shanley, Emmet Baxter ⊗ New Philadelphia, Ohio; Starling Medical College, Columbus, 1898; served as president of the Tuscarawas County Medical Society and the Seventh Councilor District Medical Society; for many years registrar of vital statistics in New Philadelphia; died July 21, aged 83.

Sheddan, William Joplin ⊗ Osceola, Ark.; University of Tennessee College of Medicine, Memphis, 1915; veteran of World War I; member of the city council; chief of staff at Osceola Memorial Hospital; died in West Memphis July 24, aged 65, of injuries received in an automobile accident.

Shields, Robert Mansen Jr., Staten Island, N. Y.; University of Vermont College of Medicine, Burlington, 1921; member of the Medical Society of the State of New York; veteran of World War I; president of the Rotary Club of Staten Island; life consultant at Sea View Hospital; associated with Staten Island Hospital, where he died July 29, aged 62, of a heart attack.

Sochacki, Alexander S. ⊗ Camden, N. J.; University of Pennsylvania School of Medicine, Philadelphia, 1928; member of the American College of Allergists; assistant in medicine at Jefferson Medical College of Philadelphia; on the staff of the Cooper Hospital; died July 26, aged 55, of acute coronary occlusion.

Thomasson, William Edward, Carrollton, Ga.; Atlanta College of Physicians and Surgeons, 1911; member of the Medical Association of Georgia; died in Atlanta June 30, aged 71.

Traywick, Asa Paul ⊗ Cameron, S. C.; College of Physicians and Surgeons, Baltimore, 1902; died July 26, aged 79.

Van Iderstine, Reginald, Daphne, Ala.; College of Medicine and Surgery (Physio-Medical) Chicago, 1906; died July 26, aged 86, of bronchitis and heart disease.

Waddington, Algernon Henry, Rockford, Ill.; Chicago College of Medicine and Surgery, 1912; veteran of World War I; died in the Rockford Memorial Hospital July 29, aged 76, of hepatoma of the liver with ruptured esophageal varices.

Walliker, Wilbur Myron ⊗ Clinton, Iowa; College of Physicians and Surgeons of Chicago, School of Medicine of the University of Illinois, 1902; past-president of Clinton County Medical Society; lifetime staff member of the Mercy Hospital and the Jane Lamb Memorial Hospital, where he was past-president of the staff; died July 24, aged 80, of coronary thrombosis.

Williams, Frank Spalding ⊗ Villisca, Iowa; Rush Medical College, Chicago, 1901; for many years member of the board of education of Villisca; a director of the Villisca Building and Loan Association; died July 26, aged 86.

Witherington, Albert Sidney, Munford, Tenn.; Memphis (Tenn.) Hospital Medical College, 1904; died in the Methodist Hospital, Memphis, July 20, aged 74.

Wyman, Harry Hastings, Aiken, S. C. Medical College of South Carolina, Charleston, 1897; past-president of the state board of medical examiners; served on the staff of the Aiken County Hospital; died in Rock Hill July 30, aged 83, of myocardial infarction and arteriosclerotic coronary thrombosis.

FOREIGN LETTERS

BRAZIL

Polyps and Malignancy.—Dr. Silvio Levy (*Revista do Hospital Matarazzo, São Paulo*) studied the relationship beween benign polyp of the colon and carcinoma. As evidences of such a relationship he cited the facts that both polyps and carcinomas are located in the various segments of the colon in almost equal percentage, the parallelism between the incidence of carcinomas and polyps of the colon in adults at different ages, the frequency with which the polyps are associated with rectocolic carcinoma, the transformation of nontreated polyps into carcinoma, the presence of adenomatous cells in many rectocolic carcinomas even in a late stage, and the high incidence of malignant degeneration in multiple polyposis. Patients with adenomas of the colon are believed to be more likely to develop a carcinoma of the colon than those who are free from adenomas. There is still some difference of opinion as to the criteria to be adopted by the pathologists concerning the diagnosis of malignancy in adenomas. Many of them do not recognize the existence of malignancy unless invasion of the tissue by the neoplastic epithelial elements is present, thus rejecting the concept of the confinement of malignant cells (carcinoma in situ).

The author reported a series of 67 patients with polyps of the colon. The incidence of carcinoma was 27%. One of the most important aspects of this series was the presence of malignant polyps in the first decade of life (25% of the cases). The incidence of polyps in 6,000 patients was 1.5%, which agrees with the figures of other Brazilian observers. The author recommends (1) sigmoidoscopy in every patient examined for the first time, regardless of age, (2) annual sigmoidoscopy in every patient over 40, (3) annual sigmoidoscopy and barium enema in all patients with a familial history of malignancy of the colon or with a previous polyp, even if it has been excised, and regardless of the patient's age, and (4) sigmoidoscopy and barium enema in all patients with rectal symptoms. This procedure should be repeated after six months if the first examination is negative.

Tuberculosis and Chickenpox.—The influence of chickenpox on 34 tuberculous children was studied by Dr. Paulo Vilhena de Morais (*Revista do Hospital das clínicas, São Paulo*, vol. 13, June, 1958) who concluded that (1) chickenpox rarely produces nonspecific alterations in the roentgenogram of the lungs or aggravates tuberculous foci in patients receiving specific treatment, (2) the regression of tuberculous lesions is not affected by chickenpox, (3) alterations of tuberculous sensitivity as a result of chickenpox are slight, and (4) chickenpox does not cause marked changes of the immunobiological state of tuberculous patients under specific treatment.

Neurofibromatosis.—Four patients with neurofibromatosis were studied by Franca and De Almeida, (*Arquivos de neuro-psiquiatria*, vol. 16, June, 1958). All of them had bilateral pontocerebellar tumors, an important diagnostic finding and the only manifestation of the disease in one patient who had the pure central form of the disease. In the others, with mixed types, besides various central lesions (neurofibromas, meningiomas) there were mild peripheral lesions. Intravertebral tumors originating from radicular sheaths were the cause of the initial symptoms in three patients. In the two in whom the cerebral cortex was studied, groups of atypical glial cells characteristic of the central type of neurofibromatosis were found. Two relatively rare lesions were found in the second patient (cortical angioma and hypertrophic interstitial neuritis of the brachial plexus). In patients with peripheral or intravertebral neurofibromatosis, as well as in their relatives, central lesions must be sought, especially tumors of the acoustic nerve. The diagnostic procedure of choice in such patients is ventriculography with iodized oil.

CANADA

Toxoplasmosis.—Harper and co-workers (*Canad. M. A. J.* 79:25, 1958) made a survey of the Toronto area to determine the incidence of positive skin reactions to toxoplasmin and the incidence of complement-fixing antibodies in the population. They found that the incidence of positive skin tests increased with age in the normal population, from 10% in the youngest group to 40% at ages over 35. None of the clinically normal persons with a positive skin or complement fixation test had any history or other evidence of toxoplasmosis. It would seem that inapparent and unrecognized toxoplasmosis is widespread in the Toronto area. A higher incidence of positive tests was present in medical students and laboratory workers than in the general population.

The items in these letters are contributed by regular correspondents in the various foreign countries.

Shellfish Poisoning.—Two epidemics of paralytic shellfish poisoning were reported in Canada in 1957, one in New Brunswick and one in British Columbia. Bond and Medcof (*Canad. M. A. J.* 79:19, 1958) described the New Brunswick epidemic in which 33 people were poisoned, though none died. The offenders were soft-shell clams and bar clams from the shore of the Bay of Fundy, whose toxicity is regularly assayed by the Department of Fisheries. When the toxicity rises above an arbitrary limit of 400 units, warning notices are posted and the consumption of the clams is considered dangerous. In spite of this, various persons gathered clams in full view of the notices and suffered the consequences. There was widespread variation in tolerance to doses of the toxin, symptoms including loosening of the teeth, respiratory difficulty, and numbness of the face, lips, tongue, and fingers. The speed of onset of symptoms in experiments suggested that the toxin might be absorbed through the oral mucosa.

The Surgeon's Fee.—A difficult problem arises when a visiting surgeon from the city operates on a patient in an outlying area, returns immediately to the city, and leaves the postoperative care in the hands of the local practitioner. What is the situation as regards the surgeon's fee, particularly when payment is being made in part or in whole by an insurance agency? Until recently, the reference committee of the British Columbia Division of the Canadian Medical Association has allowed some discretion in applying the general principle that the surgical fee is indivisible in such cases. Early this summer, however, a decision of the committee was published in the *Bulletin of the Vancouver Medical Association*. It has now been decided that when an operation is performed by a visiting surgeon, the surgical fee will not be divided and the surgeon will receive the total fee for the operation. When postoperative care is given by a local practitioner, he may find that the patient's insurance will not cover an extra fee for this. An editorial in the same issue criticized this directive on the grounds that division of a fee in such cases is not fee-splitting, which means getting paid for work not done, but a fair division of the reward according to the work done.

A State-Operated Diagnostic Center.—Although the province of Quebec has indicated as yet no intention to participate in the Federal-Provincial Hospital Insurance Plan, the provincial government decided to convert a former children's hospital in Montreal into a modern diagnostic center that will be the first of several to be built in the province. When this plan is put into operation, the first state-operated diagnostic center in Canada will have appeared. This is the outcome of six years of study. The new diagnostic center will be made available to general practitioners, placing at their disposal laboratory and other diagnostic facilities. The aim of the center will be to enable sick persons with insufficient financial resources to obtain a diagnosis at low or no cost and to assist family physicians in their work. This should not be taken as an indication that Quebec is heading towards state medicine, according to the premier.

Drivers' Licenses.—The Government of British Columbia worked out a scheme for obtaining a medical opinion on certain automobile drivers. Applicants for commercial chauffeurs' licenses, any persons over 70 years of age, and those under 70 years of age with a suspected medical condition contraindicating automobile driving are required to have a medical examination, but the onus is not placed on the family physician to decide whether the person is fit to drive or not. The applicant will forward the results of his medical examination to an official medical referee. The referee will review the findings and indicate whether a license should be approved or suspended, whether periodic examination should be required, or whether further examination is needed. The final decision will rest with the superintendent of motor vehicles, who will act on the recommendations of the medical referees. The government is asking for the cooperation of the medical profession during the developmental phase of this new program.

FRANCE

Treatment of Fatigue.—M. Albeaux-Fernet and coworkers (*Presse méd.* 66:1265, 1958) believe fatigue to be a minor response of the central nervous, neurovegetative, and endocrine systems to repeated aggression, as opposed to shock which represents a major response. Hormonal and metabolic investigations made it possible to divide this response into the following stages: (1) harmonious response (physiologic fatigue), (2) oscillating response, (3) discordant response (functional adrenal insufficiency), and (4) phase of exhaustion (polyendocrine involvement). The latter two stages represent pathological fatigue. Stage 2 is intermediate between acute and chronic fatigue. A series of 45 patients with stage 3 and 4 fatigue were given 20 mg. of adenosine triphosphate (ATP) intramuscularly for 20 to 40 days, followed by 25 mg. by mouth for 2 to 4 months. In patients with stage 3 fatigue ATP gave improvement of the general condition, increase in weight (by 1.5 kg. [3 lb.] as an average), a normalization of the blood pressure, and an improvement of the mental condition. ATP exerted a favorable action on various metabolites. The excitability of muscles to electrical stimulus that was diminished in 45% of the patients was re-established. Patients with stage 4 fatigue with total or partial deficiency of pituitary function benefited by ATP treatment

only when a previous stimulation of their glands, especially of their adrenals by the use of ACTH had placed their fatigue in stage 3.

Artificial Respiration for Respiratory Insufficiency.—P. Mollaret and co-workers (*Presse méd.* **66**:1271, 1958) said that pulmonary emphysema, a common finding in many chronic bronchopneumopathies, is characterized by a narrowing of the bronchioles with loss of pulmonary elasticity. It is manifested by a lengthening of the expiratory time with displacement of the respiratory situation toward breathing in. The result is an increase in pulmonary residual volume and consequently a prolonged time for the mixing of the alveolar gases and disorders in the alveolar distribution of the inspired gases. Many patients do not respond sufficiently to anti-infective, bronchodilator, hormonal, and diuretic therapy or even to oxygen, so that the only effective treatment is artificial respiration. This was used by the authors in 13 patients with acute respiratory insufficiency in the course of chronic bronchopneumopathy. In 12 of them artificial respiration restored effective spontaneous alveolar ventilation. In two death was due to a cerebral vascular accident, and in one the cause remained unknown. Of the remaining 10, one died three months later of a polydeficiency syndrome of alcoholic origin, and another showed no benefit from artificial respiration because of the severity of the bronchoalveolar lesions. He died in the second month of a cerebrovascular accident. Of the 13 patients, 8 were still alive after 3 to 16 months.

Serum Hepatitis.—Soulier and Pé (*Presse méd.* **66**:1207, 1958) studied the incidence of serum hepatitis. Of 93 hemophiliacs who answered a questionnaire, 85 had received a total of 2,926 transfusions, of which 693 were plasma only. Of 47 hemophiliacs who had received plasma, 7 developed an icterus due to hepatitis but in only 3 of them was the condition unquestionably attributable to the transfusion. The contamination rate per bottle of plasma averaged 0.4%. It was also possible to estimate the number of donors who might be carriers of the virus as about 1 in 10,700. Considering the low incidence and the mildness of the icterus observed in these patients, the risk of transmission of viral hepatitis by plasma transfusion is not excessive, and it does not seem necessary to alter the methods for preparation of plasma now in use, or its main indications (treatment of burns, hemorrhagic syndromes, and acute postoperative hydroelectrolytic disturbances).

Hodgkin's Disease.—P. Croizat and co-workers (*Presse méd.* **66**:1135, 1958) studied a homogenous series of 110 patients with Hodgkin's disease and concluded that the prognosis depends in part on the terrain in which the disease develops and on the treatment used. Classical factors are based on the stage of the disease, on the glandular locations, and the systemic signs. Histological investigations give little information as to the course of the disease, but the radiosensitivity and radioresistance of the adenopathies may have great prognostic significance. The study of the course of Hodgkin's disease was based not only on the survival time but also on the duration of the first remission, which is considered by the authors as the most reliable prognostic criterion. Thus, those patients whose first remission lasted longer than two years have a 50% chance of surviving over five years. The higher incidence in men was confirmed. Intensive radiotherapy in patients with a slow course is particularly indicated. Its combination with chemotherapy has given survivals up to 12 years.

NEW ZEALAND

Effects of Reserpine on the Alimentary Tract.—At a meeting of the Otago Medical School Research Society (abstracted in *Proc. Univ. Otago M. School* **36**:1, 1958), J. G. Blackman and co-workers reported that it is now widely believed that there is some connection between the pharmacological activity of reserpine and certain other Rauwolfia alkaloids and their capacity to release serotonin from various binding sites. It has been suggested that the gastrointestinal effects of reserpine are due to a peripheral action of circulating serotonin and this would explain why the gastrointestinal effects of reserpine are scarcely modified by vagotomy but, on the other hand, cannot be elicited in the isolated organ suspended in a bath. The most obvious of these gastrointestinal effects of reserpine is an increase in intestinal motility and gastric secretions. Some patients receiving reserpine complain of diarrhea. Reserpine aggravates the symptoms of peptic ulcer in man and may eventually cause gastric hemorrhage. Such effects as stimulation of the peristaltic reflex are known to be produced by serotonin even in low concentrations.

The authors found that a large dose of reserpine (5 mg. per kilogram of body weight, subcutaneously) produced gastric erosion in rats within 18 hours. Examination of the stomachs of treated and nontreated rats showed that certain histological changes occurred within a much shorter period of time. When given to mice, reserpine (10 mg. per kilogram of body weight, subcutaneously) produced gastric hemorrhage and melena within 18 hours. So did rescinnamine, deserpidine, and SU-3118 (a semisynthetic analogue of reserpine) when they were given in the same dosage. Certain other observations, however, led the authors to conclude that these effects of reserpine were not attributable to an increase in circulating serotonin. Gastric hemorrhage and melena were not produced by reserpine in mice that had been vagotomized at the

cardioesophageal junction, nor were they produced in mice that had been given 100 mg. per kilogram of body weight of iproniazid intraperitoneally 18 hours before the reserpine.

Since iproniazid is a powerful inhibitor of monoamine oxidase and prevents the rapid destruction of serotonin in the body, it would be expected to enhance rather than antagonize the deleterious effects of reserpine on the intestine, if these were in fact due to the local action of serotonin. Gastric hemorrhage and melena were not produced in mice that had been given a large dose (100 mg. per kilogram of body weight) of iproniazid even when large doses (10 mg. per kilogram of body weight) of serotonin were given subcutaneously in addition at frequent intervals (three times within six hours).

Medical Students and the M. M. P. I.—At the same meeting Dr. W. Ironside (abstract in *Proc. Univ. Otago M. School* 36:6, 1958) reported that one of the difficulties encountered in using the Minnesota Multiphasic Personality Inventory (M. M. P. I.) outside the United States is that the cultural backgrounds of subjects of other nationalities may give a pseudopathological significance to their test scores. Therefore, it is useful to know of any discrepancies between the test results of American and other groups. Moreover, if the M. M. P. I. is to be of any value outside the United States it should elicit consistent results from comparable groups. The group test results of 167 of 168 fifth-year male medical students in Otago (all of two successive classes) were compared with those of three groups of American male medical students who were at about the same stage in their careers. Many highly significant statistical differences in their mean scores were found. Only the scores in one clinical scale, hysteria, did not differ significantly. A close similarity of scoring was found in all scales when the two groups of Otago University students were compared.

All the men in two successive classes were tested, but one record sheet had to be rejected because of invalid responses. When the individual scores of Otago students were analyzed and interpreted, allowances had to be made for a general tendency toward higher scores except in the "hysteria" scale. It is on the "interest" scale, which has to do with general sexual attitudes, that the Otago students scored highest, more than 10 points above their next clinical scale score. Furthermore, Otago students differed most from the American students in this scale. Although concern over relationships with the opposite sex may play a more important part in Otago students' lives than is generally appreciated, post-test interviews suggested that the high "interest" score was not to be understood simply in terms of a difference between the sociosexual mores of the Otago students and those used in the construction of the M. M. P. I. If further results confirm that the M. M. P. I. consistently evokes uniform group responses from fifth-year medical students, it should be possible to establish norms and determine the purport of individual deviations from these norms.

INDIA

Hemorrhoids.—M. D. Patel (*Medical Bulletin*, vol. 3, June, 1958) used Proctocaine on 40 patients who were operated on for internal hemorrhoids and compared the results obtained with those of another series of 40 patients also operated on for hemorrhoids but on whom no Proctocaine was used. He injected 5 to 10 cc. of Proctocaine in the anal sphincter after spinal anesthesia was given. After injecting the Proctocaine, pain was minimal and the patient did not specifically complain about it. The amount of sedatives required postoperatively for pain was also less in the treated series. Removal of the tube and dressing the wound were also less painful. Rectal examination after operation met with little resistance. In only four of the treated patients was there no relief of pain. The average postoperative stay in hospital was less than in the control group and bowel movements were less impeded and, even if rectal impaction of feces occurred, manual relief was less painful in the treated group. Catheterization of the urinary bladder was also required less frequently. Only one patient developed a local abscess after the injection. The abscess ruptured spontaneously, leaving a skin tag. On the whole the results were encouraging and Proctocaine injection is recommended by the author in every operation for hemorrhoids.

Serum Proteins in Leishmaniasis.—S. Kumar and co-workers (*Journal of the Indian Medical Association*, vol. 31, July 1, 1958) studied the electrophoretic pattern of serum proteins and its relation to Napier's serum test commonly employed in diagnosing visceral leishmaniasis. The ages of the 25 patients in the series were 9 to 40. All of them had fever of variable duration and enlargement of the spleen or liver or both. Leishmania donovani were found in all sternal or splenic smears. The total serum protein values were normal. There was, however, a marked decrease in the albumin fraction associated with a raised gamma globulin in all patients. The alpha and beta globulins were not altered significantly. The albumin-globulin ratio was decreased. Gamma globulin constituted 81% of the total globulins (normal 54%). No relationship was seen between the intensity of Napier's test and variations in serum protein fractions, but in the group with a positive Napier's test all the protein fractions were reduced except the gamma globulin which was greatly increased. The total serum proteins did not show much difference in those with positive and negative Napier's test. The hypoalbuminemia may have been due to dysfunction of the liver, but the rise in gamma globulin could not

be explained. There may be an increased syntheses of gamma globulin in leishmaniasis under the influence of the causative organism which is situated intracellularly. The presence of a different protein responsible for the positive Napier's test as reported by other authors could not be demonstrated in the electrophoretic patterns obtained from these patients.

Japanese B Encephalitis.—Lapeyssonnie and Gobalakichenin (*Antiseptic*, vol. 55, June, 1958) first observed several cases of encephalitis in January and February, 1955, in the General Hospital in Pondicherry. No more such cases were seen until July and September. Five of these were reported in the article. The prodromal period was remarkably uniform, symptoms making their appearance four days before admission and consisting of headache and twitchings in the muscles of the neck and back rapidly developing either into fits or paralysis and usually leading to a hypertonia. This hypertonia was localized in the muscles of the lower jaw in three patients, leading to an erroneous diagnosis of tetanus. All five patients had generalized hypertonia to a varying extent, and this feature constituted an important point in the diagnosis of the disease. One patient went into coma and had convulsions and raised blood urea level suggestive of uremia. The paralysis was spastic. There was no fever until the end of the first week of the disease and it did not go above 102.2 F (39 C). This was important in differentiating these cases from those of acute suppurative meningitis. Two types were seen when the patients came for admission; one hypertonic simulating tetanus and the other convulsive. Lumbar puncture, although difficult, was done on every patient. The spinal fluid pressure was definitely reduced. This was a constant finding and the pressure started returning to normal with improvement in the clinical condition. Albumin was normal in four patients and raised in one. Sugar and chlorides were normal.

The fully developed stage of the disease was characterized by convulsions. This determined the diagnosis. In the typical convulsions all the muscles of the body were involved and the contractions varied from simple clonus or fibrillations to major epileptiform fits. They spread from above downwards, involving the face first and then the upper limbs and lastly the lower limbs. The frequency was extreme, sometimes even becoming continuous, but they diminished in intensity and frequency as the condition improved and were therefore important from the point of view of prognosis. One patient had acute "infectious" diabetes with glycosuria, probably of central origin, which was easily controlled with insulin. The period of resolution was prolonged and the average stay in hospital was one month. Signs of improvement usually appeared at the end of two weeks. Only one of the five patients died. Other conditions to be considered in differential diagnosis were tetanus, epilepsy, and, especially, Salmonella meningoencephalitis. The diagnosis of viral encephalitis was based on the early appearance of hypertonia and rigidity with a normal temperature and a short apyrexial prodromal period. In patients with Salmonella meningoencephalitis the temperature is elevated in the initial part of the illness. Blood culture and Widal reaction help to make the diagnosis.

That the disease was due to the Japanese B encephalitis virus was confirmed by demonstrating neutralizing antibodies in serums sent to the Pasteur Institute in Paris. The patients were given tetracycline in four or five times the usual doses. It was injected slowly into the vein in saline solution with or without dextrose. The authors stressed the need for intensive prolonged treatment and early institution of antibiotic treatment in order to reduce the mortality. All of these five cases occurred in August and September, 1955, after which no more were seen. These are the months in which 90% of the annual incidence of Japanese B encephalitis appeared in Korea, China, the Phillipines, and Japan. The virus reservoir and vector are not known.

Artificial Pneumoperitoneum in Pulmonary Tuberculosis.—B. C. Chakraborti studied 50 random cases of pulmonary tuberculosis treated with artificial pneumoperitoneum (*Antiseptic*, vol. 55, June, 1958). The age of these patients varied from 10 to 60 years; 3 were moderately advanced and 47 far advanced; 12 were unilateral and 38 bilateral; 17 had exudative lesions and 33 mixed, none had fibrotic lesions. All but one showed single or multiple cavities of variable size; 24 had a positive sputum at the time of induction of pneumoperitoneum. The left flank was usually selected for insufflating air. After a primary induction of 300 to 500 cc. of air, refills were given on the third and seventh day, followed by weekly refills of 1,000 cc. In 19 patients phrenic crush had been done previously; in 12 on the right side and in 7 on the left, the diaphragm attaining the level of the third to fifth rib anteriorly. The duration of the pneumoperitoneum varied from 10 to 49 months, the average duration in those showing improvement being two years. Antibiotics were given for a variable period to all the patients in combination. Severe hemoptysis occurred during the period of treatment in two patients. The weight increased in 38 and decreased in 12. The sedimentation rate came down to within normal limits in 46 patients but was increased in 4. The sputum was negative in 45 and occasionally positive in 5 at the end of treatment. Treatment had to be abandoned in two due to the development of right inguinal hernia in one and spontaneous pneumothorax in the other. Other complications occurring during treatment were pneumomediastinum in one and development of slight ascites in

another; 13 were classified as improved, 33 as active retrogressing, and 4 as active progressing. There were no deaths in the series. Thus improvement was observed in 46.

UNITED KINGDOM

Influenza and Sickness Claims.—The biggest influenza epidemic since the national insurance scheme began brought new claims for sickness benefits up to the record figure of 9.5 million in 1957. According to the report of the Ministry of Pensions and National Insurance for 1957, 5 million claims, or twice the average for the season, were made between late August and the end of 1957, suggesting that one in eight of the 20 million people insured for sickness benefit may have had influenza. The peak period was reached in the first week of October when 567,000 claims were made. This was 130,000 more than the highest week's figure in the 1951 influenza epidemic. It is calculated that the cost to the national insurance fund was about 28 million dollars.

Epilepsy and Annulment of Marriage.—An epileptic is not obliged to disclose that he has fits, except under certain circumstances, such as when he or she contemplates marriage. Then failure to disclose the condition to the intended spouse may later result in annulment of the marriage. Such a decree was recently given to a woman who married in ignorance of the fact that her husband suffered from epileptic fits. He did not have hospital treatment which was advised by his physician and had an attack just before the wedding ceremony. In English law recurrent attacks of epilepsy are grounds for annulment if the petitioner was ignorant of the fact at the time of the marriage, but proceedings must be started within a year of marriage, and marital relations must not have taken place with the petitioner's consent after discovery of the fact.

Painting Depicting Health Service.—Dr. G. F. Petty, of Cardiff, has painted a picture entitled "The Legend of the Health Service," expressing his feelings of frustration with the service. It is being exhibited with other works by members of the South Wales Art Society. The canvas, which took nearly a year to finish, is a doctor's nightmare. It shows the harassed physician, patients clamoring for attention, a nurse with her fingers in her ears to shut out the din, a dentist's chair containing a skeleton, a white-collared official holding up a book of regulations, above him the servants of the law, a tomb marked "General Practitioner R.I.P. 5 July, 1958," and stairs leading to a heavenly hospital board. Dr. Petty has been a general practitioner for about 20 years. He is on the Hinchcliffe Committee, which is examining prescribing costs, and is a member of the Cardiff Executive Council of the Health Service. He paints as a hobby and felt so strongly about the health service that he had to express his feelings through the medium of art.

Prevention of Recurrences of Rheumatic Fever.—Until recently, because of the fear of toxic side-effects from the long-continued administration of sulfonamides, these have not been widely used in Britain for the prevention of recurrences of rheumatic fever. Bywaters and Thomas made a five-year follow-up study of patients with rheumatic fever treated with sulfonamides daily after discharge from hospital (*Brit. M. J.* 2:350, 1958). One group of 96, which served as a control, was given no prophylaxis either in hospital or after discharge, and 88 patients, hospitalized for rheumatic fever, were given 1 Gm. daily of a preparation containing sulfathiazole, sulfadiazine, and sulfamerazine. All patients were examined every three months, careful notes were taken with special reference to sore throats and limb or joint pains, and the sedimentation rate was determined. The mean incidence of recurrences per patient per year was 5.6% in the untreated and 1.2% in the sulfonamide-treated group. There was only a slight variation from year to year in each group and no tendency for the recurrence rate to decrease with time. Drug reactions were few. Two patients complained of lassitude; two, who suffered from leukopenia, had their treatment changed to penicillin; one developed urticaria, which cleared up after penicillin was substituted. No case of streptococcic resistance to sulfonamide was encountered. Most of the toxic reactions occurred while the patients were still hospitalized. The authors believe that penicillin is preferable to sulfonamides as the risks of side-effects are extremely low. They recommend that prophylaxis be continued for at least five years after the attack or until the child has left school, whichever is the longer. If after leaving school patients are exposed to an increased risk of streptococcal infection, e. g., if they enter a university or join the armed forces, prophylaxis should be continued for a further period.

Vitamin B_{12} and Tobacco Amblyopia.—Heaton and co-workers believe that tobacco amblyopia is associated with vitamin B_{12} deficiency (*Lancet* 2:286, 1958). They found that the retina or the optic nerve is unduly sensitive to tobacco even in patients with mild vitamin B_{12} deficiency. In a study of 13 patients with tobacco amblyopia they found that the vitamin B_{12} serum levels ranged from 15 to 350 micromicrograms per milliliter (average 218). These values differed significantly from those of normal controls which ranged about a mean of 538 micromicrograms per milliliter. The usual manifestations of vitamin B_{12} deficiency may be absent because in pipe smokers and heavy cigarette smokers the amblyopia may precede the onset of anemia,

glossitis, neurological involvement, or a megaloblastic bone marrow by months or even years. Vitamin B_{12} was given to nine patients, of whom three continued smoking as heavily as before. All recovered more rapidly than would have been expected with the prohibition of smoking and vitamin B complex by mouth alone; 100 mcg. of the vitamin was given parenterally once or twice weekly for a month, then every fortnight for two months and finally at intervals of a month. The authors believe that tobacco amblyopia and the retrobulbar neuritis of pernicious anemia may be manifestations of the same condition. In some of their patients tobacco amblyopia and neurological features suggesting vitamin B_{12} deficiency were associated with abnormal liver function tests and low serum vitamin B_{12} levels. In any patients with unexplained peripheral neuropathy, myelopathy, or encephalopathy, especially if it is considered to be due to nutritional deficiency, the levels of total and of free vitamin B_{12} in the serum should be measured.

Boen and co-workers stated that the diagnosis of vitamin B_{12} deficiency could be made from the examination of the nuclear changes in the oral epithelial cells (*Lancet* 2:294, 1958). Mouth washings were centrifuged, stained with May-Grünwald-Giemsa stain, and the diameters of 100 consecutive nuclei determined. Normally a maximum of 5% of the nuclei have diameters of 14.5μ or more; in patients with pernicious anemia the figure is 26%. Giant nuclei are present in the cells from the oral mucosa of patients with vitamin B_{12} deficiency. The authors diagnosed vitamin B_{12} deficiency in a patient who had subacute combined degeneration but no changes in the blood or bone marrow. The diagnosis was made from oral smears. Treatment with vitamin B_{12} produced improvement and normalization of the nuclei of the cells of the oral epithelium within a week. No changes were seen in the hemoglobin concentration, reticulocyte count, or serum iron level. The diagnosis was confirmed by demonstrating a low serum vitamin B_{12} level.

CORRESPONDENCE

CARIES-PRODUCING POTENTIAL OF CHOCOLATE

To the Editor:—It is a general belief that high acid production in dental plaque is one of the major causes for tooth decay. A recent study (Ludwig and Bibby, *J. Dent. Res.* 36:61-67 [Feb.] 1957) on the production of acids in dental plaque after the ingestion of various solid and liquid foods showed that milk chocolate produced the most acid. It was also found that the amount of acid does not depend solely on the carbohydrate content of the food nor on the amount of food retained in the mouth. No attempt was made to explain why milk chocolate produced the most acid.

A bacteriological study of chocolate milk (Fuller, Mueller, and Swanson, *J. Dairy Sc.* 25:883-894 [1942]) gives data which presumably could serve as a possible explanation for the high acid production in the mouth after chocolate has been eaten. From that investigation it was concluded that cocoa powders or chocolate syrups added to milk definitely inhibited the growth of bacteria likely to be found in milk, with the exception of Streptococcus lactis. Furthermore, it was concluded from studies with pure tannic acid that the tannic substances of the cacao products are the agents responsible for inhibiting bacterial growth. While the tannin complex in cacao products is not definitely known, the work of Doelger (*Am. Leather Chem. A. J.* 31:46-63, 531-544 [1936]; 32:265-275 [1937]) gives credence to the latter conclusion. Doelger reported that bacteria in tan liquors are largely acid-producing organisms, with lactic, acetic, and butyric acid producers in greatest abundance, and that Streptococcus lactis is the chief producer of lactic acid.

Mueller and Kuzmeski (*J. Dairy Sc.* 27:897-901 [1944]) analyzed 18 samples of commercial cocoa powder for tannin-like substances and found values ranging from 2.6 to 15.6%. While milk chocolate was not analyzed for tannin-like substances, calculated amounts of these substances are from 1 to 2%, depending upon the milk chocolate formulation.

In the light of the results from Fuller, Mueller, and Swanson's bacteriological study of chocolate milk, one would expect milk chocolate to produce a greater amount of acid than many other foods commonly consumed. Any inhibition of nonacid producing microorganisms by tannin-like substances should increase the growth of acid producers because of lack of competition. Fuller, Mueller, and Swanson also found that the inhibition of bacterial growth was greater at room temperature (72 F) than at refrigerator temperature (43 F). Therefore, one would expect a still greater inhibition at mouth temperature (98.6 F) with a further increase in acid production.

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MEDICAL LITERATURE ABSTRACTS

INTERNAL MEDICINE

Experience with Intramuscular Digoxin. E. Fletcher and C. F. Brennan. Irish J. M. Sc. 6:273-280 (June) [Dublin].

A preparation of digoxin suitable for intravenous as well as intramuscular administration is now available, permitting investigators to study the effect on the heart of digoxin administered intramuscularly with regard to the rapidity of action and to compare the results with intravenous administration under control conditions. Twenty patients were selected for study; 18 of these patients had uncontrolled auricular fibrillation with low output failure, 2 being included as they had persistent extrasystolic arrhythmia. Ten patients with auricular fibrillation were digitalized rapidly, and their condition was maintained with intramuscularly administered digoxin. Eight patients with auricular fibrillation were selected for comparative study of intramuscularly and intravenously administered digoxin, and in 6 of these the effect of concurrent digoxin and mersalyl was observed.

A satisfactory therapeutic response was obtained in 15 of the 18 patients with uncontrolled auricular fibrillation within a period of 5 to 19 hours by the intramuscular administration of 1 to 2 mg. of digoxin, irrespective of age, body weight, degree of congestive failure, or nature of underlying heart disease. With the exception of 1 patient, the maintenance dose for the 10 patients with auricular fibrillation after rapid digitalization was 0.5 mg. of intramuscularly administered digoxin every 8 to 24 hours. In 2 patients ventricular ectopic foci were completely abolished (although the sinus rate was not affected) by digitalis action within 3 hours of administration, indicating a direct myocardial effect of digoxin. In 9 patients initial vagal slowing lasted 2 or 3 hours; it was followed by a transient rise in the ventricular rate, which was replaced within the hour by a progressive fall to a minimum level about the 6th hour.

The response of the ventricular rate in auricular fibrillation to digoxin given intramuscularly compares favorably with the response to intravenous administration, irrespective of whether the dose (1 mg.) was within the therapeutic range. When 2 cc. of mersalyl was given at the same time as 1 mg. of digoxin, the fall in ventricular rate in each case tended to be more marked than when digoxin was given alone, either intramuscularly or intravenously. In 1 instance a therapeutic response did not occur, but with the dosage used, the intravenous route was not found to be superior to the intramuscular route. The intramuscular administration of digoxin may be painful, and this factor alone may limit its value in maintenance therapy. Nausea due to the central action of digoxin occurred in 2 cases, but only after large doses of the drug had been given. Toxic arrhythmias—paroxysmal auricular tachycardia, multiform ventricular extrasystoles, and bradycardia—were observed in 3 cases, indicating the direct action of digoxin on the myocardium and necessitating its temporary suspension and the institution of potassium therapy.

Fibroma of Bronchus. J. E. Rodó. Medicina 17:247-254 (Oct.-Dec.) 1957 (In Spanish) [Buenos Aires].

Fibroma of the bronchus is a rare tumor. It is histologically benign, but its rapid growing may cause closure of the bronchus, resulting in death of the patient. The symptoms consist of asthma, pulmonary suppuration, and atelectasis. The diagnosis and, if possible, the removal of the tumor are made by endoscopy. A man, 40 years old, was hospitalized with fever and moderate dyspnea. He had chronic bronchitis, asthma, and pulmonary suppuration of 6 months' duration. Auscultation and roentgenologic examination of the chest showed a total atelectasis of the right lung, deviation of the mediastinum, and several enlarged mediastinal lymph nodes. A tumor in the main bronchus prevented the passage of the bronchoscope. A diagnosis of bronchogenic carcinoma was made, and an exploratory thoracotomy was planned, which the patient refused. The bronchial symptoms were relieved by the administration of antibiotics and sulfonamides. The picture of atelectasis was not modified. After discharge from the hospital, the patient had 10 applications of deep roentgentherapy. He also had a treatment with nitrogen mustard up to a total dose of 50 mg. Histological examination of an excised axillary lymph node, of a piece of bronchial mucosa taken during bronchoscopy, and of the sputum was

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negative for cancer. An exploratory thoracotomy was made 8 months after the first consultation of the patient. In sectioning the right bronchus, a pink polypoid tumor joined to the carina by a pedicle was extirpated. A pneumonectomy of the right lung was performed. The postoperative period was uncomplicated. Histological examination of the tumor and of the right lung showed fibroma of the bronchus, bronchial obstruction, atelectasis and sclerosis of the lung, and bronchial dilatations. The patient is in normal health 18 months after the operation.

Homozygous Hemoglobin C Disease: Report of 3 Cases. K. R. Tanaka and G. O. Clifford. Ann. Int. Med. 49:30-42 (July) 1958 [Lancaster, Pa.].

The authors report on 3 Negro women, aged 28, 32, and 67 years, respectively, with homozygous type C hemoglobin disease. All the patients had a fairly uniform clinical course, characterized by the presence of a mild but constant hemolytic anemia, with periodic episodes of jaundice which cleared spontaneously, variable degrees of enlargement of the liver, and marked enlargement of the spleen. Although fleeting arthralgias have been reported by other workers, none of the 3 patients had this symptom. The oldest patient underwent surgical treatment for an intertrochanteric fracture of the left femur caused by a fall. She had a rapid drop in hemoglobin value accompanied by an increase in bilirubin, and it is likely that she had a hemolytic crisis, perhaps precipitated by the surgical procedure. Although mild to moderate anemia was presumably present in all the patients throughout life, in none of them was it severe enough to require blood transfusions, except after the surgical procedure in the patient mentioned before. Low-grade reticulocytosis was present at times in all the patients. The outstanding hematological characteristics were the presence of numerous target cells in the blood smear, increased osmotic resistance to hypotonic sodium chloride solution, increased fecal urobilinogen excretion, slight but fluctuating icterus, mild reticulocytosis, and bone marrow studies compatible with hemolytic anemia. Hemoglobin electrophoresis in each patient revealed a 50% red blood cell survival time of 21 days. Studies of iron metabolism (ferrokinetics) utilizing radioiron (Fe^{59}) showed that the plasma iron disappearance half-time was shortened and that the incorporation of the injected tracer dose into the red blood cells was within the lower limits of normal. No hemoglobin other than type C was detected by paper electrophoresis. The diagnostic problem presented by these patients was resolved by the relation of all the clinical manifestations to the presence solely of type C hemoglobin. The possibility of homozygous type C hemoglobin disease should be considered when one is confronted with a Negro patient who has enlargement of the liver and spleen and mild hemolytic anemia without sickling, and hemoglobin electrophoresis should be performed.

Host Factors in Polycythemia Vera. A. Damon and D. A. Holub. Ann. Int. Med. 49:43-60 (July) 1958 [Lancaster, Pa.].

The authors report on 132 men and 65 women with polycythemia vera who were admitted to the Presbyterian Hospital in New York between 1937 and 1957. The average age of the patients at onset of the disease, which did not differ between the sexes or among various ethnic groups, was 53.7 years. In 1 patient, however, the disease was first diagnosed at the age of 9 years. This was one of the earliest cases on record of polycythemia vera; it was apparently primary and was unaccompanied by congenital anomalies. The patient led an active life without therapy or complications of his disease for 15 years after the diagnosis was made. The percentage of Negroes (3.6%) with polycythemia vera was significantly lower than the percentage of Negroes (16.4%) among the Presbyterian hospital population, and the percentage of Jews (33%) with this disease was significantly higher than their percentage among the hospital population. Both of these findings confirm previous impressions, but the Jewish preponderance was about 2 to 1 less than that usually quoted (4 or 5 to 1). The disease tended to be mild among the Negroes. Polycythemia vera occurred among white groups, other than Jewish, with the frequency expected from their hospital distribution.

Contrary to the impression of some of the workers that patients with polycythemia vera tend to be slender in build, no real difference was found between such patients and normal controls in height and weight; men with polycythemia vera and hypertension were stockier than those without hypertension, but the number of these patients was small. Patients with polycythemia vera did not differ from comparison series in the same hospital regarding ABO blood-group incidence, age at menarche, and age at menopause. Other disorders and complicating illnesses were associated with polycythemia vera in about the proportions previously reported; these conditions included hypertension (32%), arteriosclerosis (30%), peptic ulcer (14.5%), thromboses of extremities (9.5%), myeloid dyscrasias (7.6%), and gout (5.5%). Ten of the 15 patients with myeloid dyscrasias had received previous irradiation therapy. Uterine fibroids occurred in 13 (33.3%) of 39 women with adequate history or pelvic examination. A unique case was presented of polycythemia vera occurring coincident with fibroids, disappearing after hysterectomy, and recurring as polycythemia vera 5 years later. Hypernephroma was observed in 9 patients (4.4%); 2 of these patients have had complete hematological remissions after nephrectomy

for 2 and 11 years, respectively, to date. The indication for urologic investigations of hematuria in patients with polycythemia vera was noted.

Coronary Disease, Hypercholesterolaemia and Its Treatment. M. F. Oliver. Scottish M. J. 3:225-234 (June) 1958 [Glasgow].

The author feels that the increase in the mortality and morbidity from coronary disease is so striking that there are probably several extraneous factors contributing to it: 1. More people are living longer than at the beginning of this century, and, since coronary atheroma generally increases with advancing age, coronary disease is more likely to be a cause of death in today's older population. 2. There may have been changing fashions in death certification, and many deaths which in the past were certified as cardiovascular or myocardial degeneration are probably now registered as coronary disease. 3. Both the medical profession and the public are now more aware of coronary disease than in the '20s. This awareness has undoubtedly contributed to the increased frequency of diagnosis, which is often made erroneously. Hypercholesterolemia and other abnormalities in the circulating lipids are most marked in young patients with clinical coronary disease. It is suggested that the etiology of coronary disease is more closely related to disorders of the circulating lipids in young patients than in older patients. At present there is no really effective or acceptable method of lowering hypercholesterolemia. Restrictions or alterations of the diet are monotonous and unpleasant, but studies of the addition of unsaturated vegetable oils to the diet are encouraging. Thyroid analogues and estrogens lower hypercholesterolemia, but the former probably increase myocardial metabolism, even in the absence of any effect on basal metabolic rate, and the latter induce feminization to a greater or less degree. There is no satisfactory evidence that reduction of hypercholesterolemia reduces mortality and morbidity or that it inhibits the atherosclerotic process in man.

Anticoagulant Therapy in Acute Myocardial Infarction. R. L. Richards. Scottish M. J. 3:235-244 (June) 1958 [Glasgow].

Many workers have suggested that anticoagulant therapy can effect a significant reduction in the mortality rate in the weeks immediately after an acute myocardial infarction, and that it can also lower appreciably the number of clinically detectable but nonfatal thromboembolic complications. There have been few reports in which the effects of anticoagulant therapy upon the over-all mortality rate from myocardial infarction in 1 hospital or in a single medical unit have been studied. The author reports the results which have followed the introduction of this therapy. The clinical material consisted of patients with acute myocardial infarction admitted to the medical unit at the Western Infirmary, Glasgow, during the years from 1949 to 1956. It included not only those patients in whom the primary diagnosis was myocardial infarction but also those patients who experienced an infarction after admission for some other condition. The diagnosis was confirmed in all cases either by electrocardiography or at autopsy.

Over a period of 13 years (1944-1956) the death rate from acute myocardial infarction remained remarkably constant; about a third of the patients died in the hospital in the first few weeks. The introduction of anticoagulant therapy was not followed by a significant alteration in the mortality figures. The present series is comparable with others in respect of the incidence of thromboembolic and hemorrhagic complications. It is pointed out that, even when a policy of giving anticoagulants to all patients with acute myocardial infarction is adopted, there will always be a proportion of patients who cannot be so treated. The reasons for the high death rate and for the failure of anticoagulants to influence this are the large number of patients who die soon after admission (one-third of all deaths) and a high mortality rate in patients who, for one reason or another, cannot be given anticoagulants. The author suggests that, in some other reported series of patients treated with anticoagulants, methods of case selection may have influenced the results. To obtain convincing proof of the beneficial effects of anticoagulant therapy in acute myocardial infarction, a reduction in the over-all hospital mortality rate should be demonstrable. The present investigation has not provided the evidence necessary to support this opinion.

Coronary Arterial Occlusion and Its Myocardial Consequences in Coronary Atherosclerotic Cardiopathy (A Study of 212 Cases). J. Himbert and J. Lenègre. Arch. mal. coeur 51:441-459 (May) 1958 (In French) [Paris].

The relations between coronary and myocardial lesions were studied in 212 cases of coronary atherosclerotic cardiopathy. Investigations showed that 193 of the 212 hearts had sustained 517 occlusions, 281 of which were atherosclerotic and 236 thrombotic in origin. These occlusions were distributed as follows: anterior trunk, 211 (i. e., left coronary artery, properly speaking, 6; anterior interventricular artery, 205); right coronary artery, 167; and left coronary artery, 139. The proximal arterial segments were affected in 292 instances, the middle arterial segments in 165, and the distal arterial segments in 60. Major myocardial lesions, notably transmural infarcts, were observed in 59% of the anterior trunk occlusions, in 46% of the right coronary artery occlusions, and in 27% of the left

coronary artery occlusions. They occurred in 51% of the proximal segment occlusions, in 27% of the middle segment occlusions, and in 16% of the distal segment occlusions. They were found in 35% of the atherosclerotic occlusions and in 65% of the thrombotic occlusions. The number of myocardial lesions in each heart increases in proportion to the number of occluded branches and occlusions, so that the average number of infarcts in each heart rises regularly from 0.66 for 1 occlusion to 1.40 for 6 occlusions or more. These findings suggest that the type of arterial occlusion exerts a preponderant influence in the pathogenesis of myocardial lesions in coronary atherosclerosis.

Clinical and Laboratory Observations in an Outbreak of West Nile Fever in Israel in 1957. I.Spigland, W. Jasinska-Klingberg, E. Hofshi and N. Goldblum. Harefuah 54:280-281 (June 1) 1958 (In Hebrew with English Summary) [Tel-Aviv, Israel].

The authors report on the clinical and laboratory findings obtained from 419 patients with West Nile fever which broke out in the summer of 1957 in the Shomron area. The study concerns 297 soldiers from this area, 65 children and adults in the town of Hadera and vicinity, and 49 aged persons from homes in Ein Shemer and Pardes Hanna. Attempts to isolate the West Nile virus directly from the acute-phase blood sample and complement-fixation and neutralization tests for West Nile virus on paired serums were carried out in 247 patients. The results disclosed West Nile fever in 88.9% of the soldiers, in 46.0% of the inhabitants of Hadera, and in 53.5% of the aged persons. The clinical picture differed in the 3 groups. The course of the disease in the soldiers was characterized by fever, lymphadenopathy, and rash; in 1 patient meningoencephalitis developed. The symptoms and signs were typical but rather mild among the majority of the children of Hadera and vicinity. In several children there was involvement of the intestinal or the respiratory tract; 2 patients developed meningoencephalitis. The clinical picture of the disease in the aged was characterized by the absence of symptomatic signs typical of West Nile fever, and a high percentage of patients developed meningoencephalitis. Of 49 aged persons, only 33 had fever of varying degree and duration, while 12 exhibited severe neurological signs and symptoms of meningoencephalitis. These 12 patients recovered promptly, whereas 4 other aged patients developed impaired consciousness with signs and symptoms suggesting severe brain damage and died after a fulminating course. In 1 of these patients examination at autopsy revealed diffuse encephalitis. The appearance of complement-fixing antibodies was retarded, and the titer was lower in the aged than in the young.

Further Considerations on the Treatment of Tuberculous Meningitis. C. Giova and A. Di Ruggiero. Riforma med. 72:558-560 (May 17) 1958 (In Italian) [Naples].

The authors report on the therapeutic results in 2 groups of patients with tuberculous meningitis. A report on one group was prepared in 1954, whereas the other group included patients observed from 1954 until now. The first group consisted of 40 patients, 21 of whom died by 1954; 1 more patient died during the second relapse. The period after discharge of the patients in the first group has varied from 5 to 8 years. During this time a blind patient partially regained his eyesight, a deaf patient has remained such, 1 patient who was discharged in good mental state is mentally deficient now, and 3 women have had children without complications. These results are probably permanent.

The second group consisted of 25 patients, 10 of whom died. Tracheobronchial adenopathy was present in 9 patients, miliary process in 10, and nodular infiltration in 1. Both groups were given streptomycin calcium chloride or dihydrostreptomycin either by the oral route in daily doses of 20 or 30 mg. per kilogram of body weight or by the intrathecal route in daily doses of 1 to 3 mg. per kilogram of body weight. Isoniazid was added to streptomycin in daily doses from 5 to 10 mg. per kilogram of body weight. Eighteen patients (45%) were cured in the first group and 15 (60%) in the second. Thus, better results in the treatment of tuberculous meningitis obtained in recent years are related to a more prompt correct diagnosis of the disease and to the use of better therapeutic methods.

The Diagnosis of Cancer of the Pancreas, Biliary Tract, and Duodenum by Combined Cytologic and Secretory Methods: I. Exfoliative Cytology and a Description of a Rapid Method of Duodenal Intubation. H. F. Raskin, J. Wenger, M. Sklar and others. Gastroenterology 34:996-1008 (June) 1958 [Baltimore].

The authors describe a method of rapid intubation of the duodenum for exfoliative cytological studies and report the results obtained in 203 patients suspected of pancreatic or biliary carcinoma. A double-lumen radiopaque tube (the Diamond tube) has been found to be satisfactory. One lumen, the duodenal segment, extends 26 to 29 cm. beyond the shorter gastric section. A metal olive, weighing 2.5 to 5.0 Gm., caps the distal end of the duodenal extension. After fasting overnight, the patient is given an intramuscular injection of 160 mg. of pentobarbital 1 hour prior to intubation. The tube is passed orally for a distance of 45 cm.; the metal olive is situated in the cardia. One end of a low bench or table is raised approximately 16 in. The

patient lies head elevated in the left lateral decubitus position and slowly swallows 15 cm. of additional tubing. The excess tubing lies along the greater curvature. The patient then assumes a sitting position and bends forward at the waist as far as possible, taking several deep inspirations. This maneuver facilitates the entrance of the tip of the tube into the antrum as the anterior wall of the stomach falls away from the posterior wall. The procedure continues with the patient lying in the right lateral decubitus position with feet elevated for 5 minutes, during which time the tube will usually enter the duodenum. The patient is then placed on his back for an additional 3 to 5 minutes. During these last 2 steps, 10 to 15 cm. of additional tubing is slowly introduced. The location of the tube is determined fluoroscopically, and the tip is placed at the midportion of the third part of the duodenum. The gastroduodenal tube is then taped to the cheek to maintain position, and drainage is initiated with the patient lying on his back or right side on an examining table. Diagrams illustrate the different postures.

Duodenal entrance time can in most instances be reduced to 15 minutes. Occasionally the maneuver must be repeated because of coiling of the tube; this twisting is often due to the fact that the tube is passed too rapidly. The double-lumen tube drains the alkaline duodenal content independently of the acid gastric secretion. Pancreatic secretion should not be collected until adequate gastric drainage has been completed. The introduction of 200 cc. of air through the gastric lumen, followed by aspiration with the patient inclined toward the right lateral position, will facilitate complete emptying of the stomach. The gastric and duodenal tubes are then connected to a constant vacuum pump with pressure of 120 mm. Hg. The gastric juice is carried directly into a collecting jar and is discarded, but the duodenal aspirate is diverted by a simple trap which consists of 50-cc. plastic centrifuge tubes immersed in an ice bath. The pH of both drainages are determined repeatedly in order to insure that the collections are separate. Carcinoma was demonstrated subsequently by either surgery or biopsy or at autopsy in 43 of the 203 patients. Malignant cells were recovered in 28 of the 43 cases of pancreatic, biliary, gallbladder, and duodenal carcinoma.

The Diagnosis of Cancer of the Pancreas, Biliary Tract, and Duodenum by Combined Cytologic and Secretory Methods: II. The Secretin Test. J. Wenger and H. F. Raskin. Gastroenterology 34:1009-1017 (June) 1958 [Baltimore].

Whereas part 1 of these 2 papers was concerned with the duodenal intubation technique, the second paper is concerned with the secretion test and the combined use of these 2 methods in 199 patients with suspected biliary or pancreatic carcinoma. In addition 3 patients with carcinoma of the pancreas were diagnosed by cytological study alone, without the secretin test, although secretin was used as a stimulant; 1 other patient with carcinoma was studied with the secretin test alone. When the combined cytological-secretory method was employed, 1 unit of secretin per kilogram of body weight was injected intravenously over a 2-minute period after a 20-minute control collection period. Three 10-minute collections were placed in iced plastic tubes, centrifuged, and decanted into a graduate. The sediment was employed for exfoliative cytological examination, and the fluid for bicarbonate and enzyme analysis. With previously published standards as a guide, the secretory rate was expressed in terms of milliliters per kilogram of body weight for the 30-minute period after injection. The bicarbonate content was determined by means of the standard volumetric Van Slyke apparatus, checked against the manometric method on several occasions.

Since many studies of enzyme output in the secretin test have varied considerably, a new and extremely sensitive lipase determination was adopted instead of the more commonly used methods; the results are calculated in terms of micromoles of α-naphthol liberated per hour from a subtrate of naphthyl laureate per milliliter of original sample. The "normal" values for volume output and bicarbonate concentration were ascertained in 15 patients without pancreatic disease as compared with the results in 9 patients with proved carcinoma of the pancreas, 2 with carcinoma of the common bile duct or gallbladder, and 10 with various nonmalignant gastrointestinal diseases. Normally the volume of duodenal fluid should exceed 1.1 ml. per kilogram in the 30-minute collection period after secretin injection; the bicarbonate concentration should be 90 mEq. or greater in at least 1 of the 3 10-minute collections. The secretin test is most sensitive in tumors of the head and body of the pancreas. Abnormal results should always be interpreted with caution, as other disease entities or improper technique may give rise to "false-positive" findings. Analysis for pancreatic enzymes does not add appreciably to the diagnosis of pancreatic malignancy, and its omission will simplify the technique. Although slightly less sensitive than the secretin test, exfoliative cytology is important because of its high degree of specificity. For tumors of the biliary tract outside the pancreas, cytological examination is an excellent method of establishing the diagnosis. An 86% accuracy of diagnosis of carcinoma of the pancreas and biliary system was obtained through the combined use of the secretin test and exfoliative cytology.

Diagnostic Value of Radioactive Vitamin B_{12}. W. R. Pitney and J. B. Stokes. Australasian Ann. Med. 7:126-131 (May) 1958 [Sydney, Australia].

Patients with pernicious anemia differ from normal subjects in their ability to absorb vitamin B_{12} from the gastrointestinal tract. The absorption of radioactive vitamin B_{12} can be demonstrated in several ways. Some investigators measured the radioactivity excreted in the feces of their patients for several days after an oral dose of the vitamin. The recent introduction of radioactive vitamin B_{12} of high specific activity made it possible to measure plasma radioactivity several hours after the oral administration of the vitamin. Schilling in 1953 introduced a urinary excretion test to ascertain the absorption of radioactive vitamin B_{12}. When a small oral dose of radioactive vitamin B_{12} is absorbed from the intestine, little or no radioactivity appears in the urine. However, if a large parenteral injection of nonradioactive vitamin B_{12} is given to the patient at the same time, or a few hours after the orally administered radioactive dose, radioactivity appears in the urine together with most of the injected vitamin. The urinary radioactivity excreted in 24 hours is usually about one-third of absorbed radioactivity, and its measurement may be taken as an index of absorption from the intestine.

The authors studied the intestinal absorption of orally administered radioactive vitamin B_{12} by a modified urinary excretion test. Subjects were given a standard oral dose of 0.6 mcg. of vitamin B_{12} labeled with radiocobalt (Co^{60}). The mean 48-hour urinary radioactivity in 22 control individuals was 23.9% of the oral dose. In 5 patients with megaloblastic anemia due to folic acid deficiency, a similar mean excretion of 22.4% was found. In 15 patients with pernicious anemia in relapse, impaired absorption of radioactive vitamin B_{12} was demonstrated. The mean urinary radioactivity was 2.4%. This was increased to 19.6% when the oral dose was given with an intrinsic factor preparation. Twenty-five patients on maintenance therapy because of a previous diagnosis of pernicious anemia were studied. The diagnosis was disproved in 10 patients, who were shown to be able to absorb orally administered radioactive vitamin B_{12} normally.

The Use of the Schilling Test in the Diagnosis of Pernicious Anemia and Allied Conditions. J. Abels, M. G. Woldring, J. J. M. Vegter and H. O. Nieweg. Nederl. tijdschr. geneesk. 102:869-873 (May 3) 1958 (In Dutch) [Amsterdam].

The authors investigated the absorption of vitamin B_{12} labeled with radioactive cobalt by employing a modification of Schilling's urinary excretion technique. Their studies were made on 20 patients with pernicious anemia and on a control group of 30 patients. After giving 1 mcg. of vitamin B_{12} labeled with radiocobalt ($Co^{58(57)}$) by mouth, the patients were given flushing doses of 1 mg. of nonradioactive vitamin B_{12} by subcutaneous injection 2 hours and 24 hours later. The urinary excretion of radioactivity amounted to an average of 29.2% (a range of 14.2 to 46.4%) in the 30 normal subjects, whereas in the 20 patients with pernicious anemia only an average of 1.8% (a range of 0.1 to 4.4%) of radioactivity was excreted in the urine. Eighteen of the pernicious anemia patients were subsequently given 25 ml. of neutralized human gastric juice together with the orally administered dose of radioactive vitamin B_{12}. When this was done, the urinary excretion of radioactivity increased to an average of 21.2% (a range of 11.9 to 35.9%).

Vitamin B_{12} absorption is frequently impaired in patients with sprue. The authors found that in 4 out of 5 patients the absorption defect was not corrected by the simultaneous administration of intrinsic factor. They assume that renal dysfunction might be responsible for a decreased excretion. They conclude that the Schilling urinary excretion test of radioactive vitamin B_{12} is a reliable technique in the diagnosis of atypical pernicious anemia (neuropathy without blood dyscrasia or after remission) and in the differential diagnosis of megaloblastic anemias. They illustrate this with some case histories.

Principles of Prognosis in Patients with Hodgkin's Disease. L. Justin-Besançon, S. Lamotte-Barrillon and D. Lubetzki. Semaine hôp. Paris 34:1698-1703 (June 12) 1958 (In French) [Paris].

The authors examined from a histological and biological standpoint the duration of survival and prognosis in patients with Hodgkin's disease. Only patients in whom the diagnosis had been established by histological examination have been selected. The average time of survival in this series was 4 years and 1 month from the onset of the disease. Of 72 patients examined as to age at onset and survival, 6 were 50 years or older at onset, and 3 of them died within less than 6 months. The disease is of unfavorable character if it occurs at an advanced age, whereas in patients between the ages of 30 to 40 years it shows a more favorable course. This study reveals no statistically significant differences as to sex. Thirty-five men survived 4.29 years, whereas 39 women survived an average of 3.66 years. The average time of survival in 33 afebrile patients was 4.9 years and in 36 febrile patients 3 years. The development of the disease showed no significant difference between patients in whom mediastinal adenopathy occurred in the initial stage and those showing no mediastinal adenopathy. It is impossible to base a prognostic evaluation on the histological aspect of the lesions. The same applied to both the results of skin reaction tests and those

of protein electrophoresis which are devoid of prognostic value. In 16 patients in whom anemia was present during the initial stage of Hodgkin's disease, the survival time averaged 2.33 years, whereas in those patients without anemia the average survival time approached 4.90 years. There were no significant differences in pregnant patients or in those patients exhibiting pruritus as to age at onset and survival time. No correlation exists between duration of survival and demonstration of negative skin tubercular reaction; on the contrary, the survival time in those patients with a positive skin reaction was somewhat less than that in those with a negative reaction. Radiotherapy and nitrogen mustard therapy are considered the most effective, but the latter is accorded a somewhat higher rank in the therapeutic regimen. Dosage is variable and is of no prognostic value, as is the interval between the appearance of the initial signs and symptoms and their remission. The period of alleviation after the initial therapy is considered to be of great prognostic value. The patient is always liable to recurrences and relapses, since no form of therapy has been found that insures permanent relief from Hodgkin's disease. The existing therapeutic regimens have little, if any, effect on the duration of survival; however, they do provide some palliation.

Giant Follicular Lymphoblastoma: Its Treatment with Radioisotopes. J. H. Lawrence and W. G. Donald Jr. Ann. Int. Med. 49:1-16 (July) 1958 [Lancaster, Pa.].

The authors report the clinical and pathological findings in 12 men and 8 women, between the ages of 32 and 65 years, with giant follicular lymphoblastoma; 16 of the patients were followed to death, 2 are still living, and 2 were lost to follow-up. All the patients showed a fairly generalized involvement of lymph nodes, but the cervical lymph nodes only were initially involved in 11 patients. The spleen was enlarged in 17 patients, and the liver was enlarged in 8. Anemia was present in 14 patients, and leukopenia in 11. Three patients had absolute lymphocytosis or "lymphemia." One patient had a typical chronic lymphocytic leukemia. There was a marked lack of correlation between the duration of the disease and the relative benign or malignant appearance of the lesions histologically. Sixteen patients were treated with radiophosphorus (P^{32}). Small doses of P^{32} ranging from 1 to 5.1 mc. were given intravenously at intervals varying from 1 week to 2 months. The total dose given a single patient, successfully treated, varied from 6 to 44.3 mc. Five patients received this therapy while in the terminal stage of their illness and showed no response. Eleven patients received adequate radiophosphorus therapy. Three patients showed excellent response, with complete remission occurring in 1 and nearly complete remission in 2. Three patients showed good responses, with duration of control lasting from 7 to 20 months. Three patients showed a fair response but required additional local x-ray therapy for control. Two patients showed no response. The average duration of the disease in 10 of the 11 adequately treated patients who were followed to termination was 6.7 years, compared with the average duration of 6 years or less reported in the literature. Radiophosphorus therapy combined with local x-ray therapy, or alone, may be the treatment of choice in giant follicular lymphoblastoma and deserves serious consideration, particularly in those patients with widespread involvement.

Plasma-Transaminase Activity as an Index of the Effectiveness of Cortisone in Chronic Hepatitis. E. N. O'Brien, A. J. Goble and I. R. Mackay. Lancet 1:1245-1249 (June 14) 1958 [London].

Active chronic hepatitis is a relapsing inflammatory process believed to be a sequel to overt or subclinical viral hepatitis. The liver at autopsy presents the features of so-called postnecrotic cirrhosis. In some cases the lupus erythematosus (L. E.) cell test and the autoimmune complement-fixation test may be positive. Perpetuation of the hepatitis may depend on an immunological disorder and may be favorably modified by cortisone. In the absence of other visceral disease the level of glutamic oxaloacetic transaminase in the plasma provides a sensitive index of the degree of liver-cell necrosis.

In 10 patients with chronic liver disease, the rate of liver-cell necrosis was followed by serial estimations of glutamic oxaloacetic transaminase activity in the plasma before and during cortisone treatment. In 4 of 5 patients with active chronic hepatitis, a pronounced fall in transaminase levels coincided with cortisone treatment. In 5 patients with chronic liver disease of different etiology, there was no significant fall in transaminase value with cortisone treatment. This limited study supports the use of cortisone in acute exacerbations of active chronic hepatitis but sheds no light on the effect of cortisone on the ultimate outcome of the disease. It could be argued, however, that rapid control of the necrotic process might lessen hepatic scarring and disorganization.

Diagnostic Value of Serum-Transaminase Activity in Hepatic and Gastrointestinal Diseases. J. Pryse-Davies and J. H. Wilkinson. Lancet 1:1249-1253 (June 14) 1958 [London].

Determination of serum glutamic oxaloacetic transaminase activity is widely used as a diagnostic test in acute myocardial infarction and diseases of the liver. The liver has been shown to be the main source of serum glutamic pyruvic transaminase. The work described here was done to find out whether the determination of serum transaminase activity

should be recommended for inclusion in the routine liver-function tests. More than 1,000 determinations were done on 226 patients and 50 healthy controls. The patients included 66 with ulcerative colitis, of whom 10 had hepatic complications, 13 with obstructive jaundice, 15 with infective hepatitis, 27 with either cirrhosis or chronic hepatitis, 27 with hepatic metastases, 11 with cholecystitis, 35 with miscellaneous diseases of the intestinal tract not involving the liver, and 25 without organic disease.

The authors emphasize that the precision and sensitivity of the spectrophotometric method of determining serum glutamic oxaloacetic transaminase and glutamic pyruvic transaminase levels have been improved by the application of temperature corrections. They suggest that values over 40 serum glutamic oxaloacetic transaminase units per milliliter and 30 serum glutamic pyruvic transaminase units per milliliter be regarded as abnormal, provided that the results have been corrected to 25 C (77 F). It was confirmed that high values (more than 500 units per milliliter) for both enzymes are characteristic of infective hepatitis and carbon tetrachloride poisoning. Moderately raised values (100-300 units per milliliter) occur in obstructive jaundice, glandular fever hepatitis, and toxic hepatitis (excluding that due to carbon tetrachloride). Variable results were obtained in cirrhosis and liver metastases, but in 64% of the patients the serum glutamic oxaloacetic transaminase level was raised above normal values, whereas only about 40% showed increased serum glutamic pyruvic transaminase activity. Normal values were obtained in gastrointestinal diseases not involving the liver. The serum glutamic oxaloacetic transaminase level showed a moderate and transient rise (up to 300 units per milliliter) in myocardial infarction, but in this condition the serum glutamic pyruvic transaminase level usually remained normal. Serum glutamic pyruvic transaminase activity was thus of considerable value in confirming the hepatic origin of serum glutamic oxaloacetic transaminase in certain cases. Used critically in conjunction with other liver-function tests, transaminase determinations were extremely useful.

Contribution to the Study of Agammaglobulinemia and Hypogammaglobulinemia. M. Antonucci and P. Mugnaini. Minerva pediat. 10:427-431 (April 14) 1958 (In Italian) [Turin, Italy].

The object of this study was to determine by electrophoretic measurement the incidence of primary agammaglobulinemia and hypogammaglobulinemia in infants and children who show extreme susceptibility to bacterial infection. This series included 1,098 infants and children, ranging in age from 58 days to 12 years, who were brought for observation to the University Clinic of Modena for recurrent episodes of sepsis, infections of the respiratory tract, and pyoderma. This investigation included as control all infants under 12 months of age, because some patients with this disorder have an immunological response similar to normal persons. Absence of or a diminution in the level of gamma globulins, accompanied by a low alpha globulin serum concentration, was found in 4 infants (3.64 per mille), none of whom belonged to the control group. One infant, aged 2½ months, had agammaglobulinemia, and the other 3, who ranged in age from 2 months to 2 years, had hypogamaglobulinemia. The 4 patients were brought to the clinic because of an acute infection of the respiratory tract. Electrophoretic analysis of the serum of the relatives of the infant with agammaglobulinemia revealed normal concentration of serum components. Retarded means of producing gamma globulin were probably responsible for the disorder in this infant. He also had a low white blood cell count, which might be related to the hypoplasia of the lymphatic tissue, with the subsequent failure to produce antibodies. The infants with hypogammaglobulinemia were brought back to the clinic for observation because of bronchopulmonary disturbances several times after the discharge.

SURGERY

The Effective Level of Lumbar Sympathectomy: As Determined by Electrical Stimulation at Operation. W. C. Randall, W. J. Pickett, F. A. Folk and H. J. McNally. Ann. Surg. 148:51-58 (July) 1958 [Philadelphia].

The technique of direct electrical stimulation of the sympathetic nervous system has been applied to man. Sweating responses were recorded simultaneously from the complete circumference of the thigh, calf, and foot by the iodine starch paper technique. Sweating was widespread over the entire surface of the lower extremity in response to localized stimulation of the lumbar sympathetic system in some patients, while in others sweating was restricted to small areas, with marked variation in patterns of sweating as the position of the stimulation electrodes was shifted from one level to another. It is evident from the records of 2 different sympathetic trunks that a remarkable variation exists in the patterns of sympathetic (sudomotor) innervation of the lower extremity. In the first patient only sparse and scattered sweating was induced on any surface of the extremity, whereas profuse sweating was elicited on nearly all areas in the second patient, indicating that these segments of each of the individual sympathetic trunks contained entirely different proportions of the total number of sudomotor fibers supplying the lower extremity. The variations present in response to electrical stimulation of the same segment in different sympathetic trunks emphasize the fact that

the surgeon may not predict with assurance the extent or magnitude of sympathetic denervation which will result from extirpation of an arbitrarily designated ganglion or small segment of the lumbar sympathetic trunk, and point out the fallacy inherent in conventional procedures which dictate the extirpation of the same segment of the lumbar trunk in all patients.

Chronic Regional Enteritis: A Survey of One Hundred Twenty-Six Cases Treated at the Massachusetts General Hospital from 1937 to 1954. B. B. Jackson. Ann. Surg. **148**:81-87 (July) 1958 [Philadelphia].

This study represents a survey of 126 cases of chronic regional enteritis treated at the Massachusetts General Hospital, Boston, from 1937 to 1954. The patients, 48% of whom were males, ranged in age from 10 to 77 years, with a mean age of 24 years. The stomach and the duodenum were not involving the entire colon and occurred from 3 to areas in 25% of the patients. The colon was involved in 43%; 14 cases showed ulcerative colitis involving the entire colon and occurring from 3 to 19 weeks after the diagnosis of regional enteritis; 31% of the cases involved the cecum and ascending colon; 5% had disease in the transverse colon; another 5% had involvement of the descending colon; and 7% manifested enteritis in the sigmoid. The terminal ileum in its distal 15 to 20 cm. was involved in 55 (44%) of the patients, the remaining 56% having enteritis above this level in the terminal ileum, with one-third presenting proximal skip areas. Sixty per cent of the patients demonstrated a right lower quadrant mass, and 28% gave evidence of internal fistulas by x-ray study. The diagnosis of regional enteritis can be suspected from the clinical history, the symptom complex usually consisting of malaise, easy fatigability, chills and fever, weight loss, right lower quadrant mass, periumbilical cramps, and frequent, foul, mushy stools. A right lower quadrant mass and/or rectal abscess, fissure, or fistula with the aforementioned symptom complex point toward regional enteritis. The diagnosis can be made and confirmed by means of sigmoidoscopy, barium enema, and study of the small intestine, in that order. The over-all picture of malnutrition was discernible in approximately 50% of the cases; microcytic hypochromic anemia appeared in 51%; macrocytic hyperchromic anemia was observed in 4 cases; hypocalcemia was seen in 25%; tetany was noted in 12%; and frank avitaminosis was observed in 11% of the patients in spite of supposedly adequate vitamin intake.

In this series partial obstruction of the small intestine was the indication for operation in 93%, hemorrhage in 2%, perforation in 1%, and fistula in 4%. The mortality in 57 short-circuiting operations was 7%, and 4.5% in 86 resections. Obstruction at the site of anastomosis was revealed in 14% of 143 operations. Only one-third of the patients proved to have regional enteritis at reoperation; obstruction in the remaining two-thirds was due to scar formation. An appendix can be excised safely in regional enteritis only if the ileocecal junction and the proximal 30 cm. of terminal ileum are free of disease, as the drainage of an abscess adjacent to loops of intestine with regional enteritis frequently (24 of 30 cases in this series) leads to a fecal fistula. Intractable anorectal complications are most satisfactorily handled with a permanent sigmoid colostomy. In the follow-up period, which ranged from 2 to 26 years, the recurrence rate averaged 35%, spontaneous remissions being observed in 1.6%. Resection gave good results in 60 of 86 patients, as did excision of the terminal ileum and ascending colon in 70% when the disease process was restricted to this region, while segmental resection yielded favorable results in 50%. Short-circuiting procedures gave good results in 52% of 48 patients, and medical treatment alone provided good results in 35% of 22 patients. The most virulent forms of regional enteritis occur in the second and third decades of life, and the poorest results from all types of therapy occur in the same period. Patients free from the disease process longer than 4 years are considered to be permanently cured.

High Defects of the Atrial Septum. F. J. Lewis. J. Thoracic Surg. **36**:1-11 (July) 1958 [St. Louis].

Of 66 patients operated on for atrial septal defects at the department of surgery of Northwestern University Medical School in Chicago, a high defect was observed in 7 female and 5 male patients, between the ages of 5 and 52 years. The high defect should be distinguished from the foramen ovale defect and from the persistent ostium primum defect because of its unique anatomic features. It is located just inferior to the superior vena cava. The superior edge of the atrial septum in this area is a sharp crescent which forms the inferior margin of the defect, but superiorly the defect has no definite margin, since there is no remnant of the septum above it. This defect is invariably associated with a partially anomalous, pulmonary venous drainage. In the first 2 of the 12 patients the diagnosis was made only in retrospect. In the third patient, there was a foramen ovale defect in addition to the high defect, so that the author was forced to see that the high defect was a separate lesion; since then the high defect was recognized without trouble in the remaining 9 patients.

The defect was repaired with the aid of a row of sutures placed so that the aberrant pulmonary veins were directed into the left atrium as the defect was closed. The defect was repaired through an incision in the upper part of the atrium and the

lower part of the superior vena cava. There were 2 operative deaths among the 12 patients with high defects. Death resulted in a 55-year-old man from irreversible ventricular fibrillation on the operating table and was attributable to hypothermia, the technique used for these open heart operations. The second patient, a 26-year-old man, died of thrombosis of the superior vena cava, a complication peculiar to the repair of this particular type of defect. Thrombosis originating at the site of the repair may occlude the superior vena cava as well as the pulmonary veins. Such complications occurred in 4 of the 12 patients. In order to avoid these complications one can forego complete correction of the defect by leaving the abnormal connection of the right superior pulmonary vein to the superior vena cava. The patient on whom this type of operation was performed obtained an excellent clinical result, and his heart decreased in size. This operative technique is perhaps the safest method of repair at the present time. Another alternative to be explored involves anastomosis of the superior vena cava to the right atrium; this technique was used in 12 dogs, and the anastomosis was studied with angiograms in 7 animals. It remained open in 6 of these, but the follow-up was not long enough to be satisfactory.

Atypical Symptom-Sign Complex of Acute Pancreatitis. J. L. Donhauser and N. H. Bigelow. Am. J. Surg. **96**:61-65 (July) 1958 [New York].

Abdominal pain, vomiting, and shock of varying degree, such as the catastrophic "pancreatic drama" described by Dieulafoy, are looked upon as typical of acute pancreatitis. However, a clinical review of cases with autopsy findings reveals that some severe attacks causing death show little of the picture given by Dieulafoy. An analysis of the clinical records of 21 patients, verified by autopsy, was undertaken by the authors to ascertain how often an accurate diagnosis was made or at least how often it reasonably could have been made. Four of the patients reviewed had no pain. Among the other patients pain was localized in the epigastrium in 4, in the right upper quadrant in 3, and in the left upper quadrant in 1; it was generalized over the abdomen in 6 and was precordial in 1. One patient was in shock, and 1 in coma. Thus, the site of pain or even its absence cannot be relied upon. Shock was present in only 3, and vomiting in only 10 of the 21 patients. Abdominal tenderness was noted in 15 of the patients. Rigidity of the abdominal muscles was present in 7 patients. Ten patients were obese, and 4 were addicted to alcohol.

The use of laboratory tests cannot be overemphasized. Hyperglycemia without glycosuria is an important sign. Although a rise in the serum amylase level may occur in various diseases, first consideration should be given to the possibility of acute pancreatitis. Pancreatitis may be mistaken for cardiovascular disease, as was the case in 8 of the patients in this series. There may be a direct relation between the pathological condition of the cardiovascular system and pancreatitis. Electrocardiographic signs of heart disease were present in 5 of the 8 patients. The serum amylase content had been ascertained in only 1 of the 8 patients in whom pancreatitis had been mistaken for cardiovascular disease. In any type of upper abdominal disorder of uncertain or obscure nature, determination of the serum amylase value should be made.

Tuberculous Fistula of the Esophagus: Two Cases Successfully Treated by Surgery. D. V. Pecora. J. Thoracic Surg. **36**:53-57 (July) 1958 [St. Louis].

The author reports on a 48-year-old man and on a 26-year-old man with a tuberculous fistula of the esophagus, who were operated on at the State Tuberculosis Hospital in Ray Brook, N. Y. Both patients received antituberculous drug therapy which was undoubtedly important, since the tuberculous disease had become inactive in both patients by the time surgery was performed. Traction diverticula occurred in the upper thoracic esophagus as a result of adjacent tuberculous adenitis in both patients. The late appearance of symptoms referable to the esophagus and the presence of a traction diverticulum seemed to indicate that infection was the prinicipal causative factor for the fistula in the first patient. Pott's disease preceded the formation of the traction diverticulum in the second patient and probably was the causative factor for the diverticulum as well as the fistula.

A modified Schede thoracoplasty was performed on the first patient. The esophageal fistula was identified, but it was inaccessible in the apex of the pleural space. Attempts to free the esophagus were unsuccessful because of extensive scarring. Five days later, a Witzel jejunostomy was performed. Two months after the surgical intervention, an esophagogram with iodized oil failed to reveal an esophageal fistula. In the absence of obstruction of the esophagus, healing of the fistula occurred rapidly. In order to defunctionalize the esophagus, a Stamm gastrostomy was performed on the second patient, and 3 weeks later the cutaneous fistula was excised down to the esophageal diverticulum. The excision of the fistula was unsuccessful, probably because of poor drainage of the diverticulum as a result of partial obstruction of the esophagus below that level. Since the patient did not wish to accept a permanent gastrostomy, a total esophagoplasty by means of the intrathoracic ascending colon was performed according to Mahoney and Sherman's technique to permanently defunctionalize the esophagus. The esophagus was not severed near

the cardia. At the time of his discharge from the hospital, the patient was able to take a regular diet without difficulty.

Tuberculous esophagitis and its complications will sometimes heal with antituberculous drug therapy alone. However, surgical intervention may be necessary to correct mechanical factors, in which case every effort should be made to preserve as much esophageal function as possible. Occasionally, it may be necessary to create a bypass. Under these circumstances it does not seem necessary to extirpate the diseased organ.

Ganglioneuroma of the Cervical Autonomic System. N. P. D. Smyth and V. P. Perna. A. M. A. Arch. Surg. 77:39-46 (July) 1958 [Chicago].

A 20-year-old white male patient was operated on for removal of a ganglioneuroma of the left superior cervical sympathetic ganglion. The patient was reported, on follow-up study 1 year later, as still experiencing the Horner syndrome that commenced postoperatively. This is the 32nd instance of a documented cervical ganglioneuroma. The tumor occurs with equal frequency in either sex at any age but is twice as common in children, the vagal tumor occurring only in children. Twenty-six of the 31 cases reported in the literature involved 1 or more of the sympathetic ganglions; 1, the carotid body; and 4, the ganglion nodosum of the vagus nerve. Excision is the treatment of choice to be followed by irradiation in the event of malignancy. Horner's syndrome, permanent paralysis of the vocal cord on the affected side, and transient tachycardia and dysphagia are possible sequelae.

Percutaneous Left Ventricular Puncture with Catheterization of the Aorta. H. A. Fleming, E. W. Hancock, B. B. Milstein and D. N. Ross. Thorax 13:97-102 (June) 1958 [London].

Percutaneous puncture of the left ventricle for the assessment of patients with aortic stenosis has been carried out in 115 patients, and the technique itself was extended to include catheterization of the aorta via the left ventricle. It is desirable to catheterize the aorta for 2 reasons: 1. Pressure tracings recorded continuously during the withdrawal of the catheter tip from the aorta to the left ventricle may reveal the presence of an otherwise undetectable subvalvular stenosis. 2. The systolic pressure gradient across the aortic valve is calculated more accurately from the aortic pressure pulse than from a peripheral arterial pulse. The catheter entered the aorta in 28 (78%) of the 36 cases immediately and without ventricular irritability. In 1 instance the catheter could penetrate only the subvalvular chamber, and in 2 other cases in which the aorta could not be entered autopsy revealed that the valvular orifice was tiny and situated peripherally in a great craggy mass of calcium. In 4 of the remaining 5 failures there was a significant degree of aortic regurgitation. In the present series 5 cases of subvalvular obstruction have been identified, none of which have yet come to operative confirmation. There were only 2 deaths attributable to left ventricular puncture in a total of 115 cases investigated. The classical postpericardiotomy syndrome occurred in 2 instances, which responded readily to prednisone therapy. A small number of patients suffered from severe pericardial pain at the time of the puncture, which was treated with intravenously administered pethidine and has not been accompanied by any other signs. The authors suggest that this procedure be confined to patients in whom congenital subaortic stenosis is suspected, those without calcium in the valve, and those with a history of systemic hypertension.

Clinical Observations and Concepts on Mitral Commissurotomy. Huang Minh-Hsin, Chiang Shao-Chi and Yü Kuo-Juei. Chinese M. J. 76:415-425 (May) 1958 [Peking, China].

The authors report on 231 mitral commissurotomies performed in the past 3 years. The movement of the major valve in the diaphragmatic-type valve lesion is responsible for the snappy quality of the first heart sound and for the opening snap. These 2 sounds can be abolished by pressure exerted on the major valve, although pressure exerted against the minor valve induced no such change. In tight mitral stenosis it was not unusual to find these 2 sounds well localized over the left axillary region due to hypertrophy and clockwise rotation of the right ventricle. Satisfactory therapeutic results have been observed in 105 (86%) of the 122 patients followed more than 6 months after operation. Three of the 105 patients were operated on because of a rapidly progressive cardiac decompensation within 5 months of parturition with gratifying results. Hoarseness in 1 of the 3 patients with hoarseness of voice subsided within 1 month. Two patients with tight mitral stenosis, who presented mild jaundice of dual origin (hepatocellular and obstructive) and did not respond to medical treatment, completely recovered within 10 days of the operation. No improvement could be discerned, either subjectively or objectively, in 17 patients (14%). The factors responsible for the unsatisfactory results in this series are as follows: 1. Cardiac function was only slightly improved; thus, minimal or no subjective improvement was noticed postoperatively. 2. A moderate to marked degree of mitral insufficiency occurred in 6 patients, and none of them showed appreciable benefit from operation. 3. Coexisting aortic involvement occurred in 6 patients. 4. Incomplete separation of adherent valves or mere digital dilatation of the stenotic valve afforded only temporary improvement, with subsequent recurrence of all signs and symptoms. 5. The presence of rheumatic activity

either preoperatively or postoperatively gave poor operative results. The following postoperative complications were observed in a follow-up of 122 cases: auricular fibrillation, 39 (32%); paroxysmal auricular tachycardia, 3; embolization, 4; pulmonary edema, 2; postoperative neurosis, 6; gynecomastia in male patients, 10; appearance of milk secretion in females, 3; and postcommissurotomy syndrome, 29. Cardiac arrhythmias were fairly common during mitral commissurotomy. Ventricular flutter, which developed during clamping of the pericardium in 2 cases, terminated after rapid completion of valvulotomy. Chloroquine was found to be satisfactory in checking the various cardiac arrhythmias after mitral commissurotomy. No correlation was obtained between the number of Aschoff bodies in the auricular biopsy materials of 166 cases and rheumatic activity. Thrombotic changes involving the auricular appendage were present in 34%. In 10 cases of auricular fibrillation, 8 showed the presence of thrombus material.

Prognosis in Cancer of Lung. K. Winge. Danish M. Bull. 5:147-152 (May) 1958 (In English) [Copenhagen].

The material discussed is from the Central Dispensary for Tuberculosis serving the municipality of Copenhagen with its population of about 750,000. Compiled for the period from August, 1935, to December, 1955, it consists of 1,102 cases of bronchogenic cancer of the lung in 999 men and 103 women, with 70% of the patients aged from 50 to 69 years. Of the total number, 826 patients had been referred to the Central Dispensary by their physicians; 183 patients were found on group examinations among apparently healthy persons; 55, on control examinations; and 38, on mass miniature roentgenography. Of the patients in the 3 last-named groups, 100 had had symptoms, sometimes marked, for a shorter or longer time, but had remained at work with recourse to medical aid. No less than 926 (or 84%) of the patients had had symptoms prior to the demonstration of the first suspicious roentgenograms in the Central Dispensary. By far the most common symptom was cough in 89% of the patients; hemoptysis or blood-tinged sputum occurred in 24.4%; dyspnea, in 20%; pain, in 27%; and more indefinite symptoms of fatigue and loss of weight, in 41% and 26% respectively. The operability in cases with symptoms was approximately 25%, irrespective of the duration of the symptoms. Of the patients found on group examinations, 117 had been without symptoms; here 61 cases (or 52.1%) were operable. In evaluating the results, only the 982 cases diagnosed before January, 1955, are included; the shortest period of observation is thus nearly 2 years. Segmental resection, lobectomy, or pneumonectomy was performed in 270 patients (or 27.5%). The 176 patients examined from 1935 to 1944 have died. Of the 806 patients examined from 1945 to 1954, 67 survive; 62 have undergone operation, but 5 were considered to have inoperable disease. Of the 62, 5 have survived for 9 years, 3 for 8 years, 6 for 7 years, 7 for 6 years, 8 for 5 years, 8 for 4 years, 8 for 3 years, and 17 for 2 years. In the 1950-1954 period, 36.5% of the patients could be operated on radically. In 1955, recent cases of cancer of the lung were found in 120 patients; in 1956, 140 new cases were diagnosed. General practitioners are urged to send patients with catarrhal symptoms to tuberculosis dispensaries without delay and also all patients with hemoptysis, pain in the chest, and pneumonia, particularly the recurrent type of pneumonia.

Cardiomyectomy: Suggested Surgical Treatment of Cardiospasm According to Heller. W.-E. Schmidt. Chirurg 29:268-272 (June) 1958 (In German) [Berlin].

In the early forms of cardiospasm conservative methods are usually adequate. These include psychotherapy, medicinal treatment, and methods inducing local dilation. These methods prove adequate in about 80% of the cases. When conservative methods prove ineffective, surgical treatments become necessary. The author lists 17 different surgical methods that have been recommended for the treatment of cardiospasm, and suggests that Heller's cardiomyotomy is probably the most promising, particularly if it is carried out by a transthoracic approach. Operations that involve an anastomosis, that is, Sauerbruch's transthoracic and Heyrovski's abdominal esophagogastrostomies, are also valuable, particularly in the presence of esophageal dilatation not likely to regress. Most of the other surgical methods are only of historical value or are applicable only in exceptional situations. The author compared the results obtained with the aforementioned 3 methods on the basis of 841 cases collected from 38 authors. Heyrovski's method produced favorable results in 61% of the cases in which it was employed, Sauerbruch's method in 52%, and Heller's method in 86%.

Occasional failures of Heller's operation are due to inadequate description of the technique in textbooks or to the fact that the freeing of the esophagus or the myotomy was inadequate. A patient with an especially severe form of cardiospasm, with almost complete stenosis of the lower esophageal portion of the cardia, induced the author to extend Heller's operation. The patient was a 64-year-old woman. A sinistrotransthoracic exposure revealed extensive pleuropulmonary adhesions. After the mediastinal pleura had been opened, it was found that an indurated plaque, 1 cm. in thickness, surrounded the esophagus but was especially wide on the anterior side, reaching from the hiatus, a handbreadth above it, and probably continued below

the hiatus. The diaphragm was slit, and in order to rule out a malignant lesion, a gastrotomy was performed. After a transverse incision had been made into the extramucosal layer of the esophagus immediately above the constriction, a plaque, measuring 12 by 2 cm., was resected down toward the hiatus, care being taken not to injure the mucosa. Four months after the operation roentgenoscopy revealed a free passage. Histological examination of the surgical specimen revealed displacement and reduction of the muscular elements, edema, round-cell infiltration, and sclerosing inflammation. The advisability of such an extensive section of the wall may be questioned, but it was necessary to free the esophagus, and the result justified it.

Clinical Patterns of Peptic Ulcer After Sixty. C. W. Cutler Jr. Surg. Gynec. & Obst. **107**:23-30 (July) 1958 [Chicago].

While peptic ulcer develops most frequently in patients in the active middle years of life, a considerable number of patients seek relief from the distress of gastric and duodenal ulcers and their complications after the age of 60 years. This was exemplified by the fact that 430 of 3,049 patients with peptic ulcer whose cases were recorded at the Roosevelt Hospital in New York during the 16 years from 1940 through 1955 were hospitalized after they were 60 years old. This group included 319 men and 111 women. Duodenal ulcer existed in 286 patients, gastric ulcer in 126, marginal ulcer in 10, and both duodenal and gastric ulcers in 8. During the same period 176 patients past 60 years of age were admitted for cancer of the stomach. The incidence of malignant neoplasm was 41% higher than that of gastric ulcer. The gastric ulcers were localized on the lesser curvature in 121 patients and on the greater curvature in 5. Of the duodenal ulcers, 34 were deep, penetrating the intestinal wall, and in 6 instances they invaded other organs. The presence of arteriosclerosis was recorded in 186 (or 43%) of the patients. Relatively few ulcers developed for the first time after the age of 60, and these often manifested themselves by severe hemorrhage or by perforation sometimes without premonitory complaint. The most frequent of the late complications of ulcer creating a true emergency was hemorrhage, and in a fair proportion of cases bleeding had occurred before, perhaps periodically, over a period of years. Cases in which bleeding was the first ulcer symptom occurring after the age of 60 were likely to be particularly severe. Perforation of the stomach or duodenum was the second serious emergency in point of numbers, and it usually occured in old and chronic cases of ulcer and less frequently as the result of late-developing ulceration. Obstruction of the stomach, while a less acute emergency, still demanded active treatment. These patients had long-standing ulcer complaints. There was a larger group of patients with symptoms of many years' duration whose tolerance had been exhausted and who sought relief from the intractability of the ulcer.

Hemorrhage, especially if massive or recurrent, demanded surgical intervention. Subtotal gastrectomy was justifiable and safer than permitting continuance of bleeding, and in the great majority of such cases it was successful. In perforation of the stomach or duodenum, simple closure was the safest operation. In obstruction and intractability, unless the patient's status was favorable and there was reasonable assurance of the safety of subtotal gastrectomy in the individual case, it seemed best to be content with the employment of a less hazardous, if less ideal, procedure except when cancer was suspected. In hemorrhage, unless massive and continuing or recurrent, in obstruction of moderate degree, and in many cases of intractability—except perforation—the results of medical therapy, as distinct from surgery, were often adequate.

Results of Gastrectomy for Ulcer: Statistics of 400 Cases. A. Bonniot, J. Bonnet-Eymard and Y. Bouchet. Lyon chir. **54**:343-353 (May) 1958 (In French) [Lyon].

The Hoffmeister-Finsterer gastrectomy was performed on 400 patients with gastroduodenal ulcer. The immediate results were as follows: postoperative deaths, 1.5%, and postoperative complications, 3.5%. Eleven patients died later of different causes. Follow-up of 255 patients over a period of from 2 to 11 years showed that 238 (93%) recovered completely and that 74% were free from complications of any kind. Half of the patients have recovered more than their preoperative weight, and of the other half only 10% failed to recover their preoperative weight. Ninety per cent have resumed their regular work, but 10% have had to look for an easier occupation. Pulmonary tuberculosis developed in 7 patients, but this was apparently not due to the operation, because there is often a connection between pulmonary tuberculosis and gastric ulcer for which no operation has been performed. The Hoffmeister-Finsterer gastrectomy appears to be a successful operation; the risks are very slight, and it is highly probable that the results will be good.

Late Results after Gastric Resection According to Pólya. O. Noring. Nord. med. **59**:694-698 (May 15) 1958 (In Danish) [Stockholm].

From 1944 to 1953, 184 gastric resections were performed according to Pólya's method on patients with ulcers (95 of them being 50 years of age or over) at the Central Hospital in Hillerø. Fifteen patients had been operated on earlier because of a perforated ulcer, 36 had had complicating disorders before the operation, and in 13 the ulcer had

undergone malignant degeneration. There were 5 postoperative deaths. Of the 166 patients with benign ulcer, 161 were followed up in 1957; 96 reported complete freedom from symptoms, 54 were improved, and 11 were not improved. Of the remaining 5 patients, 1 had died as the result of a traffic accident and 1 of coronary thrombosis; 3 were not traced. Slight or moderate dumping symptoms were present in 3.1% and recurrent ulcers in 1.2%. The investigation confirms that the prognosis is good in patients with pyloric stenosis. The author concludes that, in the face of the grave ulcer complications of hemorrhage, pyloric stenosis, and malignant transformation, there is no better treatment than the surgical, and even considerable nervous or neurotic features in the patients do not, as a rule, constitute decisive contraindications.

Arterial Aneurysms of the Internal Carotid Artery and Its Bifurcation: An Analysis of 69 Aneurysms Treated Mainly by Direct Surgical Attack. G. af Björkesten. J. Neurosurg. 15:400-410 (July) 1958 [Springfield, Ill.]

The author reports on 30 male and 35 female patients, between the ages of 11 and 68 years, with 60 aneurysms of the internal carotid artery and 9 aneurysms of the carotid bifurcation, who were admitted to the department of neurosurgery of the Finnish Red Cross Hospital in Helsinki. Two of the 65 patients had bilateral aneurysms, and 1 had 3 aneurysms on the same side. Seventeen patients were not operated on; 11 of them died, and all but 1 died of recurrent hemorrhage. Four patients were treated by ligation of the internal carotid artery. Three of them had an infraclinoid and 1 had a supraclinoid aneurysm. Two patients tolerated the operation well and did well 6 and 5 years, respectively, after the ligation; in the other 2 patients the ligature had to be reopened because of hemiplegia, and 1 of them died. In the remaining 44 patients, 46 aneurysms were attacked intracranially. Nearly all the operations were performed with the aid of intratracheal anesthesia and controlled hypotension with trimethaphan (Arfonad). Ligature of the aneurysmal stalk with linen thread or with a silver clip was performed whenever possible. There were 4 operative deaths. Of the 40 patients surviving the intracranial operation, 2 died during the follow-up period which varied between 3 months and 4½ years. Both these deaths were regarded as caused by the operation. Thus, the total mortality rate was 14%. Twenty-one patients made a complete recovery, with their work capacity fully restored. The work capacity was impaired in 10 patients, and 1 patient was totally disabled. The advantages of direct surgical attack on aneurysm of the internal carotid artery are stressed. In an addendum the author reports briefly on an additional 33 patients with aneurysms of the internal carotid artery, in 18 of whom ligature of the aneurysmal stalk was performed with thread or clip. None of the 18 patients died. Postoperative hemiparesis occurred in 1 of the 9 patients in whom the aneurysms were clipped, and hemiplagia caused by postoperative thrombosis occurred in 1 of the 9 patients in whom the aneurysms were ligated with thread.

Complications in the Surgery of Internal Carotid Artery Thrombosis. L. J. Lemmen, J. S. Davis and L. L. Radnor. J. Neurosurg. 15:438-446 (July) 1958 [Springfield, Ill.].

The authors report on 3 men and 1 woman, between the ages of 36 and 60 years, with thrombosis of the internal carotid artery as a manifestation of diffuse vascular disease, who were operated on at the Veterans Administration Hospital in Pittsburgh in an attempt to alleviate neurological symptoms which followed complete thrombosis of this vessel. Thrombectomy was performed on the first patient with bilateral thrombosis of the internal carotid artery, resulting in facial palsy and hemiplegia on the right side, but there was no retrograde flow of blood from the internal carotid artery, and the neurological findings did not change from those on admission. In the second patient with complete left central facial palsy and spastic hemiplegia on the left side, complete occlusion of the internal carotid artery was found and a thrombus, 2 cm. in size, was removed. During removal of the clot the internal carotid artery was torn, and this vessel was closed by sutures at the bifurcation. An anastomosis of the external carotid artery to the internal carotid artery was made above the site of the thrombosis. Three weeks after the operation exploration of the anastomosis disclosed a complete thrombosis of the common, internal, and external carotid arteries. Removal of a thrombus from the proximal and distal ends of the bifurcation did not result in a flow of blood. Ten months later the patient had increased spasticity in the left leg and arm. The third patient had complete motor aphasia, ptosis of the left eyelid, right-sided facial weakness, hemiparesis on the right side, and hypesthesia over the right half of the body; percutaneous angiography revealed an occlusion of the left internal carotid artery. A thrombus, 5 cm. in length, was removed from the vessel, but no retrograde blood flow was obtained, and repeated angiography on the operating table revealed a block in the artery at the base of the skull. On reexploration a thrombus was found between the previous opening in the internal carotid artery and the common carotid artery. The internal carotid artery was torn during removal of the thrombus. Left frontal osteoplastic craniotomy with the aid of hypothermia revealed a thrombus in the supraclinoid portion of the internal carotid artery. Hemiplagia and aphasia persisted, and the patient died 1 week after the

surgical intervention. The fourth patient had sudden onset of aphasia, right-side facial palsy, and hemiparesis on the right side. Percutaneous angiography revealed a complete occlusion of the left internal carotid artery and partial occlusion of the external carotid artery. A thrombus, 6 cm. in length, was removed through a 1-cm. incision in the common carotid artery, 0.5 cm. below the bifurcation. Fair retrograde bleeding occurred from the external and internal carotid arteries, but an angiogram made on the operating table revealed a persistent occlusion in the internal carotid artery. An additional clot was removed from this vessel, followed by brisk bleeding from the vessel. The patient was given heparin intravenously after the first thrombus was removed. There was progressive improvement in neurological findings, and the patient's condition was maintained with warfarin (Coumadin) sodium, there being daily determinations of prothrombin time. Death occurred suddenly on the 10th postoperative day. Autopsy revealed multiple hemorrhages as a result of a vascular diathesis incident to the anticoagulant therapy.

Thrombectomy does not alter the basic pathological process of diffuse vascular disease, so that further symptoms from this disease may be anticipated. Limitations in surgical therapy were demonstrated in the first patient with bilateral thrombosis of the internal carotid artery and in the third patient with intracranial extension of the thrombosis of the cervical internal carotid artery. The advantages of thrombectomy through the common carotid artery were indicated in the fourth patient. Retrograde flow of blood from the internal carotid artery was not an index of complete removal of the thrombus, and the importance of concurrent angiography is emphasized. The hazards of anticoagulant therapy after successful thrombectomy were illustrated by the fatal hemorrhages observed at autopsy in the fourth patient.

Nephrogenic Hypertension (Goldblatt Kidney) Following Operative Trauma to the Renal Artery. R. R. McDonald, D. E. Szilagyi, and R. F. Smith. Circulation. 18:71-75 (July) 1958 [New York].

The authors report on a 59-year-old man admitted to the Henry Ford Hospital in Detroit for the evaluation of an asymptomatic aneurysm of the abdominal aorta that was verified by a translumbar aortography. During the dissection of the anterior surface of the aneurysm, approximately 2 cm. distal to the level of the left renal vein, an artery, 5 mm. in diameter, was inadvertently incised. This was immediately repaired without incident by means of 3 interrupted 5-0 arterial silk sutures. Further dissection identified this artery to be an aberrant main right renal artery. The aneurysm was then resected and replaced with a fresh aortic homograft. During the immediate as well as the later postoperative period, the patient developed malignant arterial hypertension, as well as a thrombosis of the right renal artery. The patient was cured by right nephrectomy.

The thrombosis of the right renal artery after operative injury set off a chain of events closely duplicating the arterial hypertension observed by Goldblatt after constriction or occlusion of the renal arteries in experimental animals. The resulting hypertension was severe, fulminating, prolonged, and resistant to treatment by hypotensive and ganglion-blocking agents; it was associated with pulmonary edema, myocardial infarction, and impairment of the renal function. Nephrectomy brought about a return of the blood pressure to normal levels. The concentration of renin in the removed kidney was 34 times greater than normal.

Clinical and Surgical Aspects of Pancreatic Pseudocyst: Analysis of Fifty-eight Cases. J. M. Waugh and T. E. Lynn. A. M. A. Arch. Surg. 77:47-54 (July) 1958 [Chicago].

In the authors' series of 58 cases there were 35 men and 23 women. Forty-eight of the patients were between the ages of 30 and 60 years, and 4 patients were less than 25 years old. A pancreatic pseudocyst developed in 3 of the latter after trauma to the abdomen. The 2 etiological factors more commonly associated with the development of a pseudocyst of the pancreas are inflammation and trauma. Inflammation is considered to be the forerunner of a pseudocyst more often than trauma, as 15 patients were found to have had acute or subacute pancreatitis at the time of operation, 6 other patients had a preoperative diagnosis of acute pancreatitis, and 37 patients presented histories compatible with recurrent episodes of acute pancreatitis. Twelve patients were found to have pathological conditions of the biliary tract at operation, 7 of the 12 presenting stones in the common duct. Eleven patients gave histories of excessive consumption of alcohol, and in 2 patients a perforating peptic ulcer was thought to have initiated the pancreatitis. Six patients related the onset of their symptoms to an episode of severe trauma.

In this series 31 patients had severe pain, 21 had moderate or mild pain, and 6 had no pain; 5 of these had a palpable mass in the abdomen, and 1 had jaundice. The pain, reported as being intermittent in nature with a wide variation in frequency and duration by 36 patients, was located in the epigastric region in 34 patients, in the left upper quadrant in 9, and in the right upper quadrant in 17. Only 2 patients reported having pain in the lower part of the abdomen. Pain extending straight through the body to the back was experienced by 15 patients. Vomiting was present in 9 patients, and evidence of high intestinal obstruction was the prominent symptom in 6. Of the 58 patients, 35

had a palpable mass at examination, and the presence of a mass was questioned in an additional 3. The mass, when present, was found in the upper portion of the abdomen in all cases, being located in the epigastrium in 14, in the left upper quadrant in 14, and in the right upper quadrant in 10. Jaundice of the obstructive type was present in 5 patients, and 12 of the 58 patients were found to have diabetes mellitus. Roentgenologic examination disclosed a mass in the upper part of the abdomen in 21 patients, and 9 patients had evidence of calcification in the region of the pancreas. A preoperative diagnosis of pancreatic pseudocyst was considered in 28 of the 58 cases in this series in contradistinction to the 9 preoperative diagnoses reported by Brilhart and Priestley in a study of 44 cases.

A variety of procedures has been employed in the surgical management of pseudocyst of the pancreas. In the reported series of 58 patients, incision and drainage were employed in 23 cases, incision and marsupialization in 17, complete excision in 9, internal drainage in 8, and evacuation of the cyst in 2. Total extirpation of the cyst gives excellent results but is seldom feasible because of its adherence to surrounding structures and to the pancreas itself. External drainage of the cyst is the treatment of choice in the majority of cases. Recurrence of the cyst can be prevented by drainage for a sufficient period of time. Internal drainage, although a more extensive procedure, may be the procedure of choice in selected cases.

Three Years' Experience with Peripheral Arterial Grafts of Crimped Nylon and Teflon. W. S. Edwards and C. Lyons. Surg. Gynec. & Obst. **107**:62-68 (July) 1958 [Chicago].

In the department of surgery of the Medical College of Alabama, Birmingham, the first crimped nylon graft was inserted to replace an arteriovenous fistula of the common femoral artery in October, 1954. Between this date and Jan. 15, 1958, 50 additional grafts have been used in the arteries of the extremities on this service. In this series of 51 cases, replacement grafts were used in 8 arterial injuries, 1 arteriovenous fistula, 3 popliteal aneurysms, and 1 traumatic aneurysm of the axillary artery secondary to long-term use of a crutch. Restoration of blood flow was accomplished in each of these 13 cases.

Thirty-eight grafts were used as a bypass around segments of obliterative arteriosclerosis. Only those grafts with outflow into the superficial femoral, popliteal, or brachial artery were included in this study. There were 7 early graft occlusions. In the 31 patients of the arteriosclerotic group who were discharged with patent grafts, 4 grafts failed from 4 to 17 months after insertion. Three of these late failures consisted of sudden occlusions; 1 was an anastomotic leak followed by thrombosis. Forty-three of the grafts were of nylon, and in the last 7 of the bypass grafts Teflon was used. All grafts were crimped to avoid kinking. The Teflon graft is easier to handle and suture than crimped nylon and is made of the most inert synthetic fiber now known.

Experience with Shunting Procedures for Portal Hypertension. P. F. Partington. Surg. Gynec. & Obst. **107**:37-46 (July) 1958 [Chicago].

Forty patients were operated on for portal hypertension between April, 1949, and June, 1957. In all but 3 patients the operation aimed at prevention of severe recurring gastrointestinal hemorrhages. The remaining 3 patients were operated on for marked splenomegaly. This was associated with hypersplenism, purpura, and ascites in 2 and no symptoms in 1. Splenorenal or portacaval shunts were performed in 27. A shunt was considered impossible or contraindicated in the remaining 13 patients. Initially acute esophageal bleeding was treated with the Sengstaken-Blakemore tube, but recurrent bleeding, coma, and death occurred in over half of the patients so treated. Three selected patients were then treated by transesophageal ligation of varices, with cessation of bleeding and no mortality.

Criteria of suitable preparation for shunting included disappearance of jaundice and most, if not all, of the ascites, a serum albumin level of 3 Gm. or more per 100 cc., a Bromsulphalein retention of not over 25%, a hemoglobin value of 10 Gm. or more per 100 cc., and no significant bleeding for a month preoperatively. Percutaneous splenoportograms and portovenograms were useful in the selection of the most suitable shunt. Portacaval shunts were performed 12 times: side-to-side in 4 patients, end-to-side in 2, and with the interposition of a segment of superficial femoral vein in 6. Splenorenal shunts end-to-side were performed 15 times. There were 2 operative deaths. Seven additional patients died in from 10 to 60 months, none of recurrent bleeding. All but the last 3 patients operated on were followed up for between 1 and 6 years. Of the 4 patients who bled postoperatively, 2 had vein grafts, 1 had a splenorenal shunt for schistosomiasis, and 1 bled after splenorenal anastomosis until resection of a benign gastric ulcer.

Determination of Portal Pressure by Means of Catheterization of the Hepatic Vein and by Direct Puncture During Operation. E. S. Bücherl, J. Koncz and R. Bücherl. Chirurg **29**:241-245 (June) 1958 (In German) [Berlin].

The authors refer to a report by Myers and Taylor, who in 1951 demonstrated that by introducing a catheter through the vena cava and into a hepatic vein until the latter was completely occluded they were able to ascertain the portal venous pressure. The authors used this method in 32 patients. The

catheter was introduced through the right atrium and the inferior vena cava. The first object of these studies was to ascertain to what extent the pressure values that are registered in the presence of an occluded hepatic vein correspond with the actual pressure in the portal vein. "Normal values" in the blocked and (by retraction of the catheter) "deblocked" hepatic vein as well as in the inferior vena cava were ascertained in 7 patients without hepatic disorders. The values ascertained corresponded with those determined in the literature.

In patients with hypertension of the portal vein, the authors obtained somewhat higher values than had been ascertained by other investigators. The authors feel that their selection of patients was to a certain extent responsible for these differences. In 15 patients with intrahepatic portal vein hypertension, it was possible to compare the preoperatively obtained pressure values in the blocked hepatic vein with the direct measurements obtained in the portal vein during operation. The latter were generally somewhat lower than were those obtained by catheterization of the hepatic vein. The authors feel that, despite these slight differences, the catheterization of the hepatic vein can be regarded as a method that provides reliable information about the pressure in the portal vein.

Dislocation of the Atlas on the Axis: The Value of Early Fusion of C1, C2 and C3. E. Alexander Jr., H. F. Forsyth, C. H. Davis Jr., and B. S. Nashold Jr. J. Neurosurg. 15:353-371 (July) 1958 [Springfield, Ill.].

The authors report on 25 patients, between the ages of 21 months and 75 years, with fractures of the odontoid process of the axis. There were 22 men, 2 women, and 1 infant. The fractures were the direct result of motor-vehicle accidents in 16 patients. Falls from a height were the cause of the fractures in 5 patients. One patient was thrown against a building by a cow. One fracture was the result of metastasis of a carcinoma of the prostate to the body of the axis. The 21-month-old infant had either trauma to the neck at birth or an infection about the neck. One patient sustained a spontaneous fracture in association with severe rheumatoid arthritis. A decompressive laminectomy was performed on the infant. Fusion of the occiput to the 3rd cervical vertebra was performed on the patient with metastatic carcinoma. Two patients were treated by surgical fusion between the axis and the atlas only. Fusion of C-1, C-2, and C-3 was performed on 12 patients. Seven patients were treated by traction, followed by further rigid immobilization for varying lengths of time. Two patients did not receive specific treatment (immobilization, traction, or surgery) for their fractures of the odontoid process.

The infant died within 24 hours, and the man with metastatic carcinoma of the prostate died within 14 days after the operation; 3 patients treated by traction died within 13 days to 9 months after injury. Fractures of the odontoid process are associated with dislocations of the atlas on the axis and carry a high mortality if associated with acute injury to the cervical spinal cord. The immediate mortality is low if there is no severe injury to the cervical spinal cord, i. e., if the patient reaches the hospital in satisfactory neurological condition. With prolonged immobilization of the head and neck, some fractures of the odontoid process undergo solid healing apparently, but the period of disability is lengthened. Late neurological complications, with occasional death up to 30 years after unsatisfactory healing of a fractured odontoid process, have been reported frequently in the past and are serious enough to warrant operative fusion to prevent future dislocation of the atlas on the axis.

Of the 15 patients on whom operative fusion was performed, only 1 (the patient with metastatic carcinoma of the prostate) died, death resulting from a pulmonary embolus. The operative method of fusion of C-1, C-2, and C-3, with the iliac bone for grafting and, more recently, ribs from a bone bank, proved satisfactory in the 12 patients in whom it was employed. It was performed from 8 days to 3 months after injury, and the patients were followed for periods ranging from 3 months to more than 6 years. Experience gained from this relatively large group of surgically treated patients leads to the conclusion that early surgical fusion in a patient with fracture of the odontoid process protects the patient from the late sequelae of atlantoaxial dislocation. Fusion can be done with much shorter hospitalization and earlier return to useful employment than with prolonged traction and immobilization which do not assure solid healing of the fractured odontoid process.

Principles in the Surgical Management of Mass Casualties. H. H. Ziperman. A. M. A. Arch. Surg. 78:1-9 (July) 1958 [Chicago].

The medical management of large numbers of sick or injured, whether they result from epidemic disease, combat, or disaster, involves the establishment of an organization that takes into consideration every essential of proper care. This orderly process of medical management insures that, wherever possible, each patient will receive treatment in proportion to his degree of morbidity and disability, and under no circumstances will the lives of the many be jeopardized by the medical needs of the one or the few. The initial management of the injured en masse is a surgical problem entailing the sorting of casualties to determine priority for treatment, evacuation, and return to duty; it entails the emergency treatment of those wounded in order

to save life and limb; it entails the surgical treatment of those injured requiring operation; and it entails the postoperative management of those casualties submitted to surgery. Sorting is the procedure by means of which the sick and wounded are classified according to type and urgency of conditions presented, so that they can be properly routed to the medical installation appropriately equipped and situated for their care. It is a continuous procedure throughout the treatment chain and must be practiced in each installation by the most mature surgeon available. It is a flexible procedure which not only takes into consideration the over-all disaster or tactical situation but also considers changes in local medical capabilities which may alter the criteria for return to duty and the priorities for evacuation and treatment. Since the priority for treatment in years past has always been based on an unfailing source of supplies for treatment and little or no disproportion between numbers of casualties and quantity and quality of medical personnel available for treatment, the most severely wounded have enjoyed the highest and the least severely wounded the lowest priority. Prior planning for the care of mass casualties due to atomic disasters requires some modification of this priority system in order to avoid disservice to the many in favor of the few because of limited treatment facilities, inadequate supplies, and lack of medical personnel. Such a modification provides for the division of all the injured into 4 groups: (1) casualties requiring minimal treatment; (2) casualties requiring immediate care; (3) casualties whose surgical treatment may be delayed without immediate jeopardy to life; and (4) casualties whose therapy will be expectant. The treatment of casualties may be divided into (*a*) first-aid and rescue, (*b*) emergency medical treatment, and (*c*) definitive surgical treatment. All treatment is to be modified by short cuts and compromises to permit caring for the larger number of casualties per unit of time.

Improvements Made in the Results of Surgical Treatment of Hypophyseal Adenomas and Craniopharyngiomas by Preoperative and Postoperative Adrenocortical Hormone Therapy. J. Decourt, D. Petit-Dutaillis, J.-P. Michard, and E. Bernard-Weil. Presse méd. 66:971-974 (May 31) 1958 (In French) [Paris].

The increasing boldness of neurosurgeons in attacking hypophyseal adenomas and craniopharyngiomas has resulted in a higher operative mortality. Advances in surgical technique and the availability of endocrine replacement therapy justify the more radical operations now performed, but the immediate dangers of preoperative and postoperative glandular insufficiency are not always given adequate consideration. Some patients are already in a state of hypophyseal and adrenal insufficiency when they come to operation, and all are more or less so after the operation. This circumstance, more than any other, is responsible for the more or less serious reduction in the resistance of these patients to aggression. It is therefore of the utmost importance to evaluate the extent of the endocrine deficiency by thorough preoperative clinical tests and an exhaustive investigation of adrenocortical function, so that the necessary corrections can be made before and after the operation.

Data obtained from the study of 12 patients who were thoroughly explored from the endocrinological point of view and of 7 others in whom the urgency of the need for operation necessitated less complete investigation showed that a certain amount of adrenal insufficiency is the rule in tumors of the hypophyseal region. The adrenal insufficiency is clinically evident in the major syndrome of hypophyseal insufficiency, which may lead to coma quite apart from surgical trauma, and exploration merely confirms the fact. Biological exploration, however, is needed to establish the lesser degrees of insufficiency present in ambulatory patients in whom the major signs are ocular or gonadal. Adrenocortical insufficiency is apparently an important element in the fragility of these patients when they are subjected to stress of any kind, whether accidental, as in the case of infectious disease; medicamentous, as in sensitivity to alkaloids or mercurial diuretics; or, even more, surgical. Precise information on the functioning of the adrenal glands can at present be obtained only by assaying the steroids that are metabolites of the adrenal hormones. Elimination of the 17-ketosteroids, which was measured in the 12 patients who were thoroughly studied, was low in 7 and normal in 2 of those with chromophobe adenomas; in the other 3, all of whom had craniopharyngiomas, it was greatly reduced, even though 1 was leading a normal life and complained only of a few visual disturbances. Corticoid elimination was reduced in 10 patients—7 with chromophobe adenomas and the 3 with craniopharyngiomas. Some of the patients with low corticoid excretion were leading normal social and professional lives in spite of the asthenia from which they suffered. This lack of parallelism between the clinical signs of adrenal insufficiency and the elimination of the steroids emphasizes the need for biological exploration which alone permits accurate measurement of the adrenocortical deficit and so provides exact indications for hormone therapy.

The authors' patients were given intramuscular injections of cortisone according to the following schedule: 50 mg. in the morning and in the evening of the day before the operation; 100 mg. on the morning of the operation; and then 50 mg. every 12 hours for the next 48 hours. The doses were reduced to 25 mg. every 12 hours beginning with

the third day, and after the first week one injection of 25 mg., easily replaced by 2 tablets of hydrocortisone, each containing 10 mg., was given daily until the patient left the service. The doses were increased to 150 mg. daily, given in 3 injections, for the first few days in cases of severe hypopituitarism, especially in patients with craniopharyngiomas. All the patients were also given injections of desoxycorticosterone in doses of 10 mg. on the morning of the operation and 5 mg. on the next day. Significant complications (an epileptic episode followed by unconsciousness on the day after the operation, and a secondary infection controlled by antibiotics) were encountered in only 1 patient on whom the operation was difficult. The postoperative period was uneventful in the other 11 patients; no disturbances of consciousness or respiration were observed, and all the patients were able to leave the service between 10 and 15 days after operation. The excellent results obtained in this small series indicate the value of preoperative and postoperative hormone therapy as a means of lessening danger and preventing complications in the surgical treatment of hypophyseal adenomas and craniopharyngiomas.

The Operative Treatment of Hirschsprung's Disease. J. A. Noordijk. Arch. chir. neerl. 10:88-97 (No. 1) 1958 (In English) [Arnhem, Netherlands].

In Hirschsprung's disease or congenital megacolon, microscopic examination reveals normal autonomous ganglions in the distended parts and an absence of these cells in the seemingly normal sigmoid and rectum. Swenson and co-workers suggested that surgical therapy be directed against the outwardly normal-looking parts and not against the distended colon. This reasoning proved a success. Not all children with a distended colon have Hirschsprung's disease, and this makes it necessary to have a careful check-up before operating. Megacolon may occur secondary to organic obstruction, such as anal stenosis, tumor, and neurological disorders, for instance, spina bifida. Another type of megacolon is due to "colonic inertia"; a third type is caused by segmental aplasia of autonomous ganglions (Hirschsprung's disease).

The author is concerned with this last type of megacolon. He treated 11 patients, performing Swenson's operation on 9 of them. Seven of these survived without complications and are well. A rectovaginal fistula developed in 1 patient, and 1 patient died during the operation. A partial colectomy was performed on 2 adult patients, the sigmoid being removed but only the upper part of the rectum. One of these patients has had regular stools for 3 years and has no complaints. The other patient has periods in which laxatives are necessary. Only 2 of the 11 patients were women. The author recommends Swenson's type of operation. He emphasizes that the transitional zone may reach into the hypertrophic part, especially in older children. It is, therefore, necessary to make frozen sections of the intestinal wall during the operation in order to determine where the normal ganglions begin.

NEUROLOGY & PSYCHIATRY

One Thousand Cases of Late Onset Epilepsy. S. Sheehan. Irish J. M. Sc. 6:261-272 (June) 1958 [Dublin].

All the patients in this series of 1,000 patients, comprising 632 males and 368 females, who experienced their first attack of unconsciousness at or after the age of 20 years, have been followed up for periods varying from 6 months to 10 years. Sixty of the patients when first seen had had only 1 epileptic attack; the remaining 940 had had 2 or more attacks. The age range for the entire group extended from 20 to 76 years. In 24 of these patients a history of epileptiform disturbance in some member of the family was elicited. An air encephalogram or a cerebral arteriogram or both were obtained in 950 patients.

Of the patients studied, all those with rapidly growing and highly anaplastic cerebral gliomas were dead within 6 to 15 months of their first seizure. Excluding those who died of primary or secondary neoplastic processes, 11 patients died as a result of coronary thrombosis, 1 was a suicide, and 2 died in nonconnected accidents. Seventeen patients whose clinical state was that of presenile dementia died within 5 years of hospital admittance for investigation of seizures. There were 106 patients (10.6%) with primary cerebral tumor in this series, 74 of whom were male. Primary bronchogenic carcinoma with metastatic spread accounted for 24 of the 33 patients who had seizures due to metastases. The patients in the cerebral arteriosclerotic and hypertension group numbered 71, and those in the carotid thrombosis and stenosis group totaled 15. The cases of 3 patients, all male and in their early 50's, with middle cerebral artery thrombosis were confirmed angiographically. The association of migraine and epilepsy was noted in 109 patients; many in this group had had migraine headaches for years before they had an attack of unconsciousness. The number of patients in the post-traumatic group reached 73, 60% of their attacks having commenced within 6 to 9 months after injury, which was most commonly a closed head injury. The neurosyphilis component was comprised of 17 males and 10 females, all of whom had acquired syphilis and were in the secondary and tertiary stages of the disease with the exception of 3 with congenital syphilis. Disseminated sclerosis was seen in 25 patients in association with fits. Three patients with congenital hemiplegia, which

included 2 instances of agenesis of the corpus callosum and 1 of toxoplasmosis, developed focal seizures in their 20's, and 2 had abnormal air encephalograms showing porencephaly and ventricular dilatation on the side of the brain affected. One of the 5 alcoholics had hypertension, arteriosclerosis, and Korsakoff's psychosis; 2 others had a Wernicke type of encephalopathy from which they made a good recovery. There were 3 patients with brain abscesses, 2 secondary to chest infection and 1 to mastoid infection.

Five patients, ranging in age from 20 to 35 years, experienced their first epileptic attacks during their first pregnancies, 4 other patients having had their attacks during their second and third pregnancies. In no case was there any evidence of albuminuria or hypertension or other factors that could be attributed to toxemia of pregnancy. Other etiological factors that accounted for the attacks were as follows: diabetes mellitus, 2; hyperinsulinism, 1; subdural hematoma, 2; idiopathic hypoparathyroidism, 1; subacute bacterial endocarditis, 3; sarcoidosis, 1; leukemia, 2; internal hydrocephalus, 3; pernicious anemia, 1; excessive beer consumption, 3; and superimposed chest infection, 5. An etiological factor has been established in 552 cases (55%), and of these primary and secondary tumors constituted 139 (25%).

The last group (idiopathic epilepsy) was composed of the remaining 440 patients (44%) in whom no specific etiological factor had been demonstrated at the time of investigation. In this group 50 patients, none of whom had less than 3 verified grand mal attacks, had discontinued treatment of their own accord without any recurrence of their attacks. The most common medicament employed in this group was phenytoin sodium and/or phenobarbitone. Primidone (Mysoline) has been used to some extent, but the incidence of toxic effects and intolerance has proved to be high. A new glutonamide derivative known as Preparation 16038, which is the 9-(*p*-aminophenyl)-α-ethyl glutonamide, has been on trial either on its own or with other anticonvulsants. The preparation, which has been shown to be helpful in patients in whom no other combination of treatment had been effective thus far, appears to be relatively nontoxic, and no blood dyscrasias have been noted as a result of its use.

Myasthenia Gravis After Removal of Cystic Thymus: Study of Electrolytes During Myasthenic Crisis. E. Fongi, D. Gotlieb, C. A. Vaamonde and others. Prensa méd. argent. 44:3754-3760 (Dec. 27) 1957 (In Spanish) [Buenos Aires].

A thymectomy on patients with myasthenia gravis results in great improvement of symptoms. The development of myasthenia gravis of a rapidly fatal course after removal of an aberrant thymus has not been previously reported. A woman, 22 years old, complained of anorexia, loss of weight, constant midsternal pain, and cough. These symptoms had lasted a year. On hospitalization the patient appeared normal, except for loss of weight. There were no signs of myasthenia gravis. Roentgenologic examination of the chest revealed a mediastinal shadow. At operation a cyst was removed, which on histological study proved to be an aberrant cystic thymus. The patient reported 4 years after the operation, complaining of difficulty in mastication, deglutition, respiration, and walking. Her face and general appearance were those of one with myasthenia gravis. Several acute crises occurred, with the patient hospitalized. These were controlled by intramuscular administration of Prostigmin in doses of 0.25 mg. at intervals of 8 hours and later by intramuscular administration of Pyridostigmine in doses of 1 mg. at intervals of 4 hours. Improvement of the patient permitted another operation to be performed, during which an enlarged thymus was found and was removed. Histologically it proved to be a hyperplastic persistent thymus. The patient died in an acute respiratory crisis 36 hours after the operation. In the course of the crisis a study of the electrolytes was carried out. The potassium in the blood plasma was normal. This study showed that the good results of potassium therapy in myasthenia gravis are due to the decurarizing effect of potassium on neuromuscular impulses, rather than to a correction of a special disturbance of potassium in myasthenia gravis, which does not exist.

Electroencephalographic Abnormalities in Hepatic Insufficiency and in Coma. J. Bogacz, M. Arcos Pérez and E. García Austt. Acta neurol. latinoam. 3:364-373 (No. 4) 1957 (In English) [Buenos Aires].

Hepatic insufficiency in primary diseases of the liver produces in all cases severe neurological and neuropsychiatric disorders, the most serious of which are the disturbances of consciousness which progress into hepatic coma. Thirty-three patients with insufficiency of the liver were observed on the neurological ward of the Hospital of the Faculty of Medicine of Montevideo. Twenty-eight patients had cirrhosis of the liver, 3 had viral hepatitis, and 2 had extrahepatic obstructive jaundice. The patients had been treated with cortisone, corticotropin, antibiotics, and some of them with glutamic acid. Tests for liver function were made, and electroencephalograms were taken. The patients were placed in 4 groups according to the stage of the disturbances of consciousness: (1) alert patients; (2) clouded state of mind; (3) superficial coma (restless period); and (4) deep coma. Fourteen patients were in the second stage, 6 of these patients passed into coma (third or fourth stage), and 3 patients were in deep coma immediately after hospitalization (fourth stage). Humoral tests showed dysfunc-

tion of the liver in all cases, but the results of the tests did not change when the disturbances of consciousness became more severe. The electroencephalograms, on the contrary, showed a progressive depression of the cerebral electrogenesis, paralleling the intensification of the disturbances of consciousness. An electroencephalographic pattern characteristic of only superficial hepatic coma progressing into deep coma was found. It registers at the end of the third stage and the beginning of the fourth stage. It consists of delta polyrhythmic waves and bilateral synchronous complexes of slow spike-waves which are predominantly in the frontal region. The pattern persists all through the period of coma. In deep coma it disappears and is substituted by bilateral biphasic or polyphasic waves which are followed by the flat record of electrical silence. The flat record is not an indication of immediate death of the patient. When it lasts more than 24 hours, the patient develops unilateral or generalized epileptic seizures before death. The results of electroencephalographic studies showed that cortisone and corticotropin do not modify the electroencephalographic records. The authors conclude that hepatic coma is an authentic electroclinical syndrome in which the progressive humoral and organic changes caused by insufficiency of the liver and the reaction of the nervous system to the changes are the causal factors.

Treatment of Acute Barbituric Acid Poisoning: Ten Years' Experience at Center for Treatment of Poisoning in Copenhagen. S. Louw. Danish M. Bull. 5:137-143 (May) 1958 (In English) [Copenhagen].

Since late 1949 all patients with severe cases of barbiturate poisoning have been admitted to a special section of the psychiatric clinic of Bispebjerg Hospital, Copenhagen. The number of admissions has been about 900 annually. Treatment is supervised by psychiatrists from the clinic assisted by 3 trained nurses working on 3-shift duty. The main object of the treatment is to combat manifest and latent conditions of shock and establish physiological conditions. As fluids for infusion blood, Macrodex (a blood plasma substitute) and dry serum are used in quantities depending on the severity of the shock. Rapid intervention in various complications is of decisive importance. Since 1955 a physiological stimulant, arterenol, has been employed. If the state of shock remains uninfluenced after the first liter of intravenous infusion, arterenol is added to the infusion in doses of 4 to 12 mg. per 500 ml. of fluid. From 1946 to 1951 the mortality fell from over 24% to about 2% in Copenhagen and to an average of 3.7% for the entire country; in 1955 the total lethality for the country was 2.3%. The antidote for barbituric acid, synthesized by Shaw and co-workers, is called Megimide (Glutamisol). Until April, 1956, 7 patients with complete apnea due to poisoning with barbituric acid were treated with Megimide (partly with Amfisol), and the paresis was relieved in all cases. Tests with Megimide, continued in 1956 and 1957, confirmed the results of the first test period. Megimide has a stimulating effect on reflex activity and particularly on respiration and may thus be a valuable preparation in severe intoxication. As a stimulant it has the advantage over central analeptics previously used in that it does not cause overloading of the heart by increase in blood pressure or hyperpyrexia. The main method of treatment of acute barbituric acid poisoning continues to be the combating of circulatory shock by the infusion of fluids. Megimide will be of use in special cases, notably those complicated by respiratory paresis.

GYNECOLOGY & OBSTETRICS

Cytologic-Colposcopic Observations of the Ectocervix of Pregnancy. W. R. Lang, A. E. Rakoff and G. Tatarian. Surg. Gynec. & Obst. 107:31-36 (July) 1958 [Chicago].

The authors made studies on 300 pregnant women, evaluating the portio vaginalis of the cervix by cytological, colposcopic, and biopsy methods. One hundred ninety-eight women were examined during various stages of normal pregnancy; 81 other women were examined in the immediate postpartum period (median time after delivery, 40 hours), and 21 were studied just before or after a spontaneous abortion. The median age of all patients was 27 years. Cytological specimens were obtained both by vaginal aspiration of the posterior fornix and by cervical scraping. The smears were fixed in equal parts of 95% alcohol and ether and then stained by the method of Papanicolaou. During pregnancy the succulence of the cervix and the increased cellular desquamation tend to provide numerous cells for study. Colposcopy was done with an instrument that provided stereoscopic inspection of a well-illuminated cervix at a magnification of 10 times. Three per cent aqueous acetic acid is applied to the portio to increase detail. Aqueous iodine solution in the form of strong iodine solution (U.S.P.) (Lugol's solution) is applied as a surface vital stain to detect iodine-nonstaining areas (Schiller's test).

The major effect of pregnancy on the cervix is that the squamous epithelium may proliferate to such a degree that the surface seems wrinkled colposcopically; it may even become papillomatous. The authors observed 4 such patients, all with normal cytological smears. Ten patients had grossly visible polyps; tiny polypoid structures were frequently noted colposcopically. Squamous covering

(epidermidalization) of a polyp may also be recognized by colposcopy. Epidermidalization of cervical polypi may be associated with benign atypias in the smear. The general vaginal cytological picture of normal pregnancy is briefly described. The colposcopic picture of a cervical erosion is the same in pregnant as in nonpregnant women. The cervix during the postabortal period resembles the cervix during pregnancy, except that it is dilated and shows evidences of trauma, such as laceration, true erosion, and ecchymosis. After delivery the cervix contracts rapidly, so that by 48 hours the os is nearly normal in size. Noncancerous colposcopic atypias were noted in 22 instances. Biopsy was performed on all except 2 of these patients. The findings were: simple leukoplakia, 7 times; mosaic leukoplakia (whitening with a mosaic pattern), 6 times; inflamed transformation zone, 4 times; ground leukoplakia (whitening with a stippling of red spots), 3 times; and true erosion, 2 times. Carcinoma in situ was discovered in 1 woman, in whom the Papanicolaou smear and colposcopy remained negative during pregnancy. Invasive carcinoma was discovered in 2 women, aged 37 and 23 years respectively. Gross inspection of the cervix during the pregnant state, even more so than during the nonpregnant state, affords only a rough estimate of the true nature of the cervical changes seen. Cytological studies are valuable in the routine screening of the pregnant cervix. Colposcopy is of value in further studying those patients in whom gross changes are noted by speculum examination or those who have an abnormal smear. Colposcopy does not lend itself to a routine screening program. Both cytology and colposcopy provide diverse, yet complementary data concerning the uterine cervix of pregnancy.

Mesonephric Carcinomas of the Ovary. S. Kay and R. H. Hoge. Surg. Gynec. & Obst. 107:84-94 (July) 1958 [Chicago].

Since Schiller's original paper on mesonephroma of the ovary, considerable controversy has arisen concerning this tumor. The authors feel that the attitude of uncertainty about mesonephric tumors of the ovary is all the more surprising, since neoplasms of mesonephric origin appear to be readily accepted in other portions of the female genital tract, where Gärtner's duct may embryologically be sought. During the last 7 years, the authors had the opportunity to study 9 malignant ovarian tumors believed to be of mesonephric origin. The histories of these 9 patients are presented. From the gross appearance of the ovarian tumors there was nothing especially characteristic that would permit a diagnosis prior to miscroscopic study. The tumors were generally cystic with solid areas. Papillary structures were a feature in some neoplasms. A few of the growths showed a mucoid substance exuding from the cut surface. These tumors are characterized by tubular structures which often resemble wolffian duct tubules. Branching dichotomous tubules may prove to be a prominent feature. The tumor cells frequently show clear cytoplasm which in many instances stains positively for fat, mucin, and glycogen. An exaggeration of the cytoplasmic vacuolation leads to a picture of hypernephroid carcinoma which resembles those clear-cell carcinomas commonly found in the kidney. When vacuolation is extreme, lipid material appears to be the principal component in the cells. These neoplasms are malignant and, when they arise in the ovary, presage a grave prognosis, should capsular invasion and adherence to adjacent structures be present.

Vaginitis and Neonatal Infection: Etiology of the Mycoses of the Newborn. J. Bret and C. Coupe. Presse méd. 66:937-938 (May 24) 1958 (In French) [Paris].

Bacteriological studies of 300 consecutive mothers and their newborn infants showed that in most cases neonatal mycotic infections can be traced to vaginal mycosis in the mother. Specimens were taken from the first 200 mothers at the time of delivery, and from the last 100 both at the time of delivery and on admission to the service, as a means of determining the incidence, if any, of infection contracted in the hospital. The specimens obtained from the first 200 infants were taken at birth and 6 hours later from the oral cavity and the nasal fossae, and again 24 hours and 4 days after birth from the oral cavity, the nasal fossae, the stools, and the urine. The 24-hour and 4-day studies were repeated in the last 100 infants when they were ready to leave the service, 10 to 25 days after birth.

The percentages of positive cultures obtained in the newborn infants in these two groups were practically the same—16 and 17%. Candida albicans was not found immediately after birth in the oral cavities or nasal fossae of any of the infants born of mothers free from vaginal mycosis. Infants in whom C. albicans was present in the oral cavities or nasal fossae immediately after birth, on the other hand, were born of mothers carrying the same infection. Hospital contamination was apparently responsible for the infection in 2 infants in whom C. albicans was present at the time of discharge, although they were free from infection at birth and were born of mothers who were not infected.

The need for thorough bacteriological studies and treatment of vaginitis during pregnancy, if neonatal infection is to be prevented, is shown by the discovery of C. albicans in the vagina in 20% of the women at the time of delivery. The infection was transmitted to the infants during delivery by

83% of these women; in the other 17%, whose infants did not contract the infection, delivery was rapid (2 or 3 hours), with a short expulsive period and late rupture of the membranes. Postnatal pathological manifestations of mycosis are much less common in newborn infants than might be expected from the frequency with which C. albicans is found in their oral cavities immediately after birth. The mycotic organisms generally disappear spontaneously for some unknown reason a few days after the birth of the infant. Only 7 (40%) of the 17 infants in the second group in whom C. albicans was found at birth still harbored the infection 10 days later. The transient appearance of C. albicans in the urine of infants with no associated signs of mycosis does not necessarily indicate a pathological condition, but seems rather to show that the urinary tract is a pathway by which the organisms are eliminated.

A Clinical Trial of Intravenous Apresoline in the Management of Toxaemia of Late Pregnancy. G. T. Johnson and R. B. Thompson. J. Obst. & Gynaec. Brit. Emp. 65:360-366 (June) 1958 [London].

The authors describe their experiences with hydrazinophthalazine (Apresoline) given intravenously to 25 patients in the third trimester of pregnancy. The patients studied had toxemia in the latter weeks of pregnancy; the average duration of pregnancy was 36 weeks, with a range of 30 to 43 weeks. The ages of the patients ranged between 20 and 42 years. On admission to the hospital all remained at rest in bed throughout the study. The sodium intake was restricted to less than 1 Gm. per day, and the intake of fluid was reduced to approximately 1 to 1.5 liters per day. In 7 patients the preeclampsia was superimposed on a preexisting hypertension. In some of these the blood pressure had been elevated before the 20th week of pregnancy, and in some it was known to have existed before the onset of pregnancy.

In nearly all the patients the administration of Apresoline was preceded by a period of observation during which traditional methods of treatment were employed. Apresoline was given by intravenous injection in an initial dose of 20 mg. dissolved in 1 ml. This produced in most cases a steady fall in blood pressure, beginning a few minutes after administration and reaching a maximum in 1 to 1½ hours. The effect was maintained for 3 or 4 hours, after which a steady rise occurred, which on rare occasions reached the original level in 8 to 12 hours. In these patients treatment had to be repeated at intervals of from 6 to 12 hours. In only 3 cases were more than 3 injections given, as the need for Apresoline therapy usually arose in patients with severe preeclampsia in whom there was an indication for early induction of labor as soon as the patient's condition permitted. The authors found that intravenously administered Apresoline is capable of reducing the level of preeclamptic hypertension when it arises in the latter weeks of pregnancy, its hypotensive effect being unimpeded by preexisting essential hypertension. The drug produced normotensive levels in most patients, often when other traditional techniques had failed. The drug was most useful before surgical induction of labor, but the authors emphasize its possible danger if combined with general anesthesia. Side-effects of Apresoline were not prominent, and its hypotensive effect was superior to orthodox methods of sedation in both complicated and uncomplicated preeclampsia. A more extensive trial with short-term Apresoline treatment is justified.

Vagitus Uterinus—The Cry in the Uterus. A. Iklé. Schweiz. med. Wchnschr. 88:600-601 (June 14) 1958 (In German) [Basel, Switzerland].

A 24-year-old primipara went into labor at term. Uterine contractions developed spontaneously, and in the course of 8 hours the uterine os was dilated to the size of the palm of the hand. After that there was no further progress. In order to counteract this state the bag of waters was ruptured, and an infusion of dextrose was given. Three hours later the cervix was completely dilated, and the head of the child had reached the interspinal line when there was another arrest in the delivery. There was evidence that the pelvis was somewhat small and that the sacral concavity was somewhat flat ("lower forward sacrum"), but since the child was not large and the head could be compressed, it seemed that vaginal delivery could be expected. The Kielland forceps were to be employed, but since they could not be placed properly, it was decided to use forceps with smaller blades. While the nurse handed the instrument to the obstetrician, the infant was heard to cry, making a sound like that of a child crying under a pillow. The infant was extracted by forceps; it was not asphyctic and cried at once. There was no increased nasopharyngeal or tracheal secretion.

The author comments on vagitus uterinus and cites earlier reports on this phenomenon. It has been suggested that the following requirements must be fulfilled for this condition: 1. The bag of waters must have been ruptured. 2. Air must have entered the uterus. 3. The infantile respiratory center must have been stimulated by a strong asphyxia or pain stimulus. The entrance of air into the amniotic cavity is possible only when much of the amniotic fluid has run off and the uterus has a vacuum that can draw in external air through the vagina. This situation exists in the course of manual

or instrumental intrauterine interventions. These interventions may also involve irritation to which the infant will respond with an inspiratory or cry reflex.

PEDIATRICS

ABO Incompatibility and Haemolytic Disease of the Newborn. G. H. Valentine. Arch. Dis. Childhood **33**:185-190 (June) 1958 [London].

A survey was made in St. Thomas, Ont., Canada, in a general hospital serving a population of about 60,000 of European descent. All babies judged to show the slightest jaundice within the first 24 hours after birth were investigated. Twenty-one such infants were found among 1,000 unselected live births. Seven of these were diagnosed as being examples of rhesus hemolytic disease, and these are excluded from this series. Evidence is presented that the other 14 infants had ABO hemolytic disease. ABO hemolytic disease can occur in clinically recognizable degree as often as once in every 71 births and may arise in 7% of AB incompatible mother-child pairs. It is thus about 3 times more common than hemolytic disease due to Rh incompatibility. Despite this higher incidence, however, hemolytic disease due to ABO incompatibility is much less widely known than that due to Rh incompatibility. The failure to recognize ABO disease is due chiefly to the fact that it is usually not a serious condition. It is uncommon in its severe degree, and in its common form it is so slight as scarcely to be recognized. In rhesus disease the presence of antibody with Rh incompatibility indicates disease. It is not necessarily so in ABO disease. No immune antibody may be detectable antenatally in ABO disease, although it may appear after delivery. Unlike rhesus disease, ABO disease cannot be anticipated by antenatal testing with any certainty. There is always a reason for jaundice within 24 hours of birth. The diagnosis of "physiological jaundice" should not be invoked to explain such jaundice. The present survey showed that ABO hemolytic disease may quite often need close watching and active treatment.

Perinatal Pulmonary Pathology. J. N. Briggs and G. Hogg. Pediatrics **22**:41-48 (July) 1958 [Springfield, Ill.].

The authors present an analysis of the natural history of changes in the lungs of infants dying within the first 7 days. Of 136 infants observed at autopsy between September, 1954, and February, 1957, 110 were alive at birth and 26 were stillborn. Pulmonary factors were the chief cause of death in 68 of the 110 liveborn infants. In the remaining 42 infants pulmonary conditions were contributory factors rather than the chief cause of death. In 37 of the 110 infants a hyaline membrane was present. Histological study revealed that a definite time lapse after the infant's birth appeared to be necessary before hyaline-like atelectasis, hyaline membrane, and pulmonary hemorrhage were likely to be present in the autopsy material. Therefore, those infants who died early showed only a hyaline type of atelectasis; those who survived longer demonstrated a true hyaline membrane; subsequently, massive intrapulmonary hemorrhage, which floods the air spaces, developed. These 3 conditions reached a peak incidence between 8 and 24 hours. The incidence of pneumonia showed 2 peaks, the first occurring within 12 hours and the second after 48 hours. A new pathological condition, a hyaline type of atelectasis in the absence of a true hyaline membrane, was noted. This condition is considered to fall into the same clinical and pathological category as hyaline membrane and pulmonary hemorrhage.

The Effect of Immunization Against Influenza on an Epidemic of Respiratory Illness in Children. M. M. Glazier. Pediatrics **22**:60-64 (July) 1958 [Springfield, Ill.].

The author presents a clinical study of an attempt to control by vaccination an epidemic due to influenza virus, type A′, which occurred in and about Boston during 3 months of 1953. A group of 591 children had been routinely immunized with influenza virus (types A and B) vaccine beginning in 1946. After October, 1948, this polyvalent vaccine was supplemented with type A′ influenza virus and was used to immunize the children. The patients were divided into the following subgroups. Group 1 consisted of 128 children, aged from 4 months to 14 years, who had been immunized previously from 1 month to 4.3 years but who had not received a "booster" dose before the epidemic. Fifty (39%) of the 128 children had been vaccinated from 2 to 4 years suggesting that viral influenza immunization may be effective for years. Only 1 child of this group developed a toxic form of influenza. Group 2 consisted of 161 children, aged from 6 months to 13 years, who not only had been immunized previously but had been given a "booster" dose of 0.03 ml. of influenza virus vaccine intradermally at the onset of the epidemic. One child of this group developed a moderate form of influenza. In the current immunization series, group 3a consisted of 241 children, aged from 3 months to 18 years, who were injected with 0.03 ml. of influenza virus vaccine intradermally and a week later 0.5 ml. subcutaneously. Not a single case of influenza developed in this group that had received 2 injections of the vaccine just prior to or at the beginning of the epidemic. Of the 61 children in group 3b who received only the initial (0.03 ml.) dose of influenza

virus vaccine just before the epidemic, 7 developed an influenzal infection; 6 of these children, who ranged in age from 2 to 8 years, became ill within 7 days after the intradermal injection, and the remaining patient within 11 days. The control group in this study consisted of 122 children who because of lack of knowledge or lack of cooperation were not vaccinated; 21 of these children became ill with a moderate or severe form of influenza during this epidemic.

Isolation of a Cytopathogenic Agent Resembling the CA Virus from an Infant with Croup. H. G. Cramblett. Pediatrics 22:56-59 (July) 1958 [Springfield, Ill.].

The author reports a case which is the first substantiation of Chanock's earlier observations on the association of infection with croup-associated (CA) virus (or group of viruses) and the clinical syndrome of croup. A 4-month-old infant, admitted to the University Hospitals of the State University of Iowa in Iowa City on Aug. 15, 1957, with the diagnosis of croup, was in obvious respiratory distress. The infant was not cyanotic but exhibited suprasternal and infrasternal retractions. Inspiratory stridor and a barking, metallic cough were quite prominent. With the exception of the noisy respirations, the lungs were normal by percussion and auscultation. Despite the administration of 50 mg. of chloramphenicol per kilogram of body weight and placement of the infant in a Croupette with oxygen (4 liters per minute) and 100% humidity, respiratory stridor increased. The patient became asymptomatic after the administration of 0.5 ml. of sirup of ipecac. The cytopathogenic effect, which was first noted 10 days after inoculation of cell cultures, was indistinguishable from that caused by the CA virus and quite similar to that caused by the mumps virus. In passage, the cytopathogenic effect became apparent after 4 to 6 days of incubation. After the third passage, the titer of the virus in tissue culture was regularly $1:10^5$ TCD_{50} per milliliter (TCD—tissue culture dose). The hemagglutinating characteristics of the two viruses were also the same. Reciprocal-cross-neutralization and hemagglutination-inhibition tests suggested that the virus from the patient in this case was closely related to, if not identical with, the CA virus.

Rupture of Normal Spleen in Infant During Delivery: Hematologic Investigations During Convalescence. A. Hottinger and A. Gilardi. Schweiz. med. Wchnschr. 88:587-597 (June 14) 1958 (In German) [Basel, Switzerland].

The authors present the history of an infant who sustained splenic rupture during birth. Pregnancy had been free from complications, and labor commenced at term. Delivery proved difficult because the infant (girl) was exceptionally large (weight: 4,530 Gm. [10 lb.]; length 54.5 cm. [1 ft. 9½ in.]), and the mother was obese (110 kg. [225 lb.]). Manual extraction of the left shoulder resulted in fracture of the left clavicle. Although the coagulation was normalized by means of a synthetic vitamin K preparation, signs of shock appeared after a blood transfusion. Signs of anemia, hemolysis, and intra-abdominal hemorrhage appeared. The intra-abdominal hemorrhage was verified by puncture. Splenic rupture was suspected and was corroborated by a laparotomy. The spleen had 2 tears but otherwise appeared normal. It was removed, and the postoperative course was normal.

The blood of this infant was studied repeatedly during the first 4½ months after the splenectomy. The hemoglobin value was determined, the erythrocytes and thrombocytes were counted, and the percentages of the reticulocytes and of inner bodies were controlled. The number of normoblasts was determined at various intervals, as were also the bilirubin value and the serum iron content. The length of survival of the erythrocytes was ascertained with the aid of red blood cells tagged with radiochromium (Cr^{51}). These studies revealed about the same values in this infant who had undergone splenectomy as in normal infants of the same age. In view of the fact that the child was fed with cow's milk and did not receive iron therapy, the increase in weight was fairly rapid after the third week of life, and this seemed to indicate that the erythrocytes introduced during blood transfusion disappeared at a normal rate. The only unusual aspect of the blood picture in this infant was the appearance of inner bodies and a few Howell-Jolly bodies in a small percentage of the erythrocytes. These changes are frequently seen after extirpation of the spleen. The physical and psychological development of the child was normal. In view of the slight hematological changes observed after the splenectomy, it is assumed that the child might have an accessory spleen.

Kernicterus in Premature Infants Associated with Low Concentrations of Bilirubin in the Plasma. R. C. Harris, J. F. Lucey and J. R. MacLean. Pediatrics 21:875-884 (June) 1958 [Springfield, Ill.].

There have been a number of reports in recent years of kernicterus unassociated with erythroblastosis, the etiology of which has been variously ascribed to the hyperbilirubinemia of prematurity, anoxia, increased permeability of the blood-brain barrier to bilirubin, excess vitamin K therapy, excess oxygen, sepsis and diarrhea, liver damage, hypoglycemia, and more recently an increased concen-

tration of indirect bilirubin in the serum. All the 85 infants studied were part of a larger group study carried out by Silverman and others to test the relative effectiveness of 2 prophylactic antibacterial regimens on newborn premature infants. Kernicterus, as proved by postmortem examination, occurred in all weight groups with no relation to the fatality rate from all causes in each weight group. All the 14 surviving infants had concentrations of direct (van den Bergh) bilirubin in the plasma of less than 2 mg. per 100 cc. and peak total bilirubin concentrations of more than 15 mg. per 100 cc. at any time during the study. Only 1 of the 9 infants proved to have kernicterus at time of autopsy was found to have developed a concentration of bilirubin higher than 20 mg. per 100 cc. of plasma, and in the majority the peak value was less than 15 mg. per 100 cc. All the latter group presented at some time prior to death a clinical picture compatible with kernicterus, which included 1 or more of the following neurological signs: opisthotonos, spasticity, a "sunset" sign, poor feeding, and, terminally, a bloody discharge from the nose or mouth. A review of the patients disclosed to have had kernicterus at postmortem examination revealed that 11 of the cases had occurred in the penicillin-Gantrisin prophylaxis group of Silverman and associates. Upon completion of his studies Silverman substantiated the hypothesis that the penicillin-Gantrisin prophylactic regimen promoted the development of kernicterus in small premature infants. It was later established that, while a patient is slowly dying, the concentration of bilirubin in the plasma diminishes. In 20 infants in the penicillin-Gantrisin group, the average peak value of plasma bilirubin was 8.0 mg. per 100 cc. (S.D.±3.9) and occurred on the 3rd day of life, while in 30 infants who were given Terramycin the average peak value was 16.4 mg. per 100 cc. (S.D.±7.2) and occurred on the 4th day of life. The difference is significant and suggests that the antibiotic agents may have had a direct effect on the production, distribution, or elimination of bilirubin in the premature infants.

Chemical and Clinical Observations During Treatment of Children with Phenylketonuria. H. K. Berry, B. S. Sutherland, G. M. Guest and B. Umbarger. Pediatrics 21:929-940 (June) 1958 [Springfield, Ill.].

Three children with phenylketonuria, between the ages of 2½ and 4½ years, have been treated with 3 different diets with low-phenylalanine content during the past 18 months. An attempt was made to evaluate each child by physical examination, electroencephalographic examination, psychometric studies, roentgenographic skeletal examination, and chemical analyses of the blood at periodic intervals. Analyses of serum were made at regular intervals by means of a paper chromatographic method described by Berry. While no dramatic improvement in mental ability was observed in these children, all 3 demonstrated improved motor ability, better balance, greater dexterity, increased awareness, lengthened attention span, and decreased tenseness and irritability. In diets 1 and 3 restriction of phenylalanine was accomplished by the use of casein hydrolysates from which phenylalanine had been removed and other amino acids added. The intake of phenylalanine was limited in diet 2 by the restriction of total intake of protein in the diet. Diets 2 and 3 were commercial preparations. Nutritional disturbances were encountered as a result of amino acid deficiencies in diet 1. Inadequate caloric intake and low-protein intake contributed to poor nutritional status at 1 stage in the treatment. Biochemical abnormalities characteristic of phenylketonuria were improved when phenylalanine was restricted in the diets of the 3 children. The improvement in behavior, motor control, and ease of handling was such that the parents were unwilling for the children to receive diets with the normal content of phenylalanine.

Hydramnios as an Aid to the Early Diagnosis of Congenital Obstruction of the Alimentary Tract: A Study of the Maternal and Fetal Factors. J. R. Lloyd and H. W. Clatworthy. Pediatrics 21:903-909 (June) 1958 [Springfield, Ill.].

The authors report on 220 patients with alimentary tract obstruction of congenital origin, who were admitted to the Columbus (Ohio) Children's Hospital. Thirty of these infants (23 of the 49 infants with obstruction of the small intestine proximal to the first 15 cm. of the jejunum and 7 of the 53 infants with esophageal atresia) were delivered of hydramnic mothers. None of the remaining 118 infants whose anatomic obstruction was distal to a point 15 to 20 cm. beyond the ligament of Treitz were delivered of mothers with hydramnios. Among the 17,615 deliveries conducted at the Ohio State University Hospital during the years from 1950 to 1955, 76 cases of hydramnios occurred, which should be divided into 4 main groups. Group 1 included 30 normal healthy babies from hydramnic mothers in whom the measured amount of amniotic fluid varied from 2,000 to 3,500 ml. Group 2 included 29 abnormal infants who showed definite evidence of anatomic or functional abnormality that interfered with normal deglutition or alimentation; yet these developmental defects involving the alimentary tract were not always apparent on inspection at the time of birth. The amount of amniotic fluid in the hydramnic mothers varied from 2,000 to as much as 8,000 ml., the largest

amount being observed when the fetus had anencephaly or was stillborn and macerated. Group 3 included 13 mothers in whom the hydramnios was associated with a diffuse generalized metabolic process involving both the mother and the child; with the exception of the obvious stigmata of diabetic progeny, all the babies were viable and normal. Group 4 included 2 cases of diabetes and a single case of toxemia among the mothers, 1 mother being delivered of a viable infant with several loops of cord around the neck. Three infants were stillborn, and in each case the hydramnios of the mothers was of a severe degree (2,500, 5,000, and 6,000 ml. of amniotic fluid).

The hydramnios was of mild or moderate degree in the groups with abnormal mothers, 17% of whose offspring were malformed, whereas in the 2 groups with normal mothers nearly one-half of the fetuses were abnormal. Hydramnios appears to be of particular importance when it occurs during the last trimester of an otherwise normal pregnancy. In such instances it is frequently of a more marked degree and forebodes a major fetal anomaly in nearly half of the cases. Otherwise, normal-appearing infants who are delivered of mothers with hydramnios should be suspected of having obstructive disease. That some hidden intrinsic obstructive lesion will be found by such studies appears to be the expectation in about 14% of all cases so examined.

Minor Motor Epilepsy: Diagnosis, Treatment and Prognosis. S. Livingston, V. Eisner and L. Pauli. Pediatrics 21:916-928 (June) 1958 [Springfield, Ill.].

All socioeconomic groups were embraced in this study of 698 children with minor motor epilepsy seen at the children's epilepsy clinic of Johns Hopkins Hospital. The patients ranged in age from 3 weeks to 5½ years: 369 were males and 329 were females. Of 622 patients in the follow-up study, 220 have been followed for 3 to 10 years, and the remaining 402 for 10 to 22 years. Three types of seizures were encountered in the following order of frequency: (1) massive myoclonic; (2) head nodding; and (3) akinetic. Minor motor seizures rarely begin after the patients are 4 or 5 years of age and are frequently preceded or accompanied by major motor seizures. Of the 698 patients, 192 had 1 or 2 major motor seizures prior to the appearance of the minor motor seizures; 86 of these patients continued to have both major and minor motor seizures for a period of time thereafter, the remaining 106 having no recurrence of major seizures. Mental retardation was present in 657 (96%) of the 671 children evaluated at the age of 1 year. Clinical evidence of varying degrees of brain damage before the onset of seizures, such as developmental retardation, cerebral palsies, and impairment of vision, was exhibited by 601 (86%) of the 698 patients. A demonstrable motor defect of central origin, the most common of which was the spastic type, was apparent in approximately 50% of the patients by the time they were 2 years old. While the etiology of minor motor epilepsy cannot be definitely stated, the records reveal an association with cerebral injury or damage in 445 (68%) of the 698 patients, the most common being a cerebral birth injury (trauma and/or anoxia) which occurred in 225 (32%); 14% of the infants were premature. The second most common cause was a congenital defect in cerebral development, followed by some variety of meningitis or encephalopathy. Death occurred before the 6th year of life in 23 patients. Four deaths were due to traumatic injury associated with seizure; 3 patients died in status epilepticus; 10 patients were found dead in bed, death presumably having been caused by suffocation; and 6 died of acute infections. Only 11 of the remaining 457 patients had normal intelligence, 142 of the original 622 patients in the follow-up study having been institutionalized between the ages of 3 and 12 years. Three patients who appeared to have normal intelligence at 1 year of age now exhibited evidence of retardation. The follow-up studies would seem to indicate that the frequency of minor motor seizures tends to decrease spontaneously with increasing age and that these spells disappear almost completely by the time the patient reaches 5 years of age. However, these studies also indicate that the patient with minor motor epilepsy frequently develops other types of seizures, particularly major motor seizures, as he grows older. Only 2 of the 285 patients who were 5 years of age or older were still having minor motor seizures, 107 suffered major motor seizures, 33 had psychomotor attacks, and 143 had been free from all seizures for periods ranging from 2 to 18 years. The hypsarrhythmic pattern disappeared from the electroencephalograms of 330 of the 381 patients who previously displayed this pattern by the time they were 5 years of age and from the tracings of the remaining 51 patients before they were 7. A ketogenic diet is postulated as being the best therapy for minor motor epilepsy, complete control of spells having been obtained in 91 (49%) of 186 patients with this form of therapy.

Nephrectomy in Juvenile Hypertension Associated with Renal Disease: Report of 15 Cases. H. C. Welch, L. E. Harris and J. H. DeWeerd. Pediatrics 21:941-949 (June) 1958 [Springfield, Ill.].

In the past 20 years 15 children were subjected to a nephrectomy at the Mayo Clinic because of apparent renal ischemia and associated renal hypertension. Renal disease was interpreted as unilateral in 11 children and bilateral in 4. Nephrectomy was

ineffectual in reducing the hypertension in the latter group, even though changes were predominant in one kidney and apparently minor in the other. Transient decreases in blood pressure were noted in 3 of the 4 children, but hypertension was again severe within a year. Three were dead within 2 months to 6 years after nephrectomy, and in 1 the blood pressure was unchanged after 2½ years. Of the 11 children in the group with unilateral renal disease, 8 had an initially good response to nephrectomy, and a good late response was noted in the 6 on whom follow-up studies were available. Three patients had an equivocal early response—in all 3 prompt decreases in blood pressure were noted; however, blood pressures were not normal by Smith's criteria at the time of discharge. Two of the 3 patients have been observed for more than 1 year, and both have had a return of blood pressure to normal, indicating that failure of the blood pressure to reach normal promptly does not preclude the possibility of a later return to normal. Five of the 10 patients with an early good response or a late good response or both were found to have had chronic pyelonephritis. Three others had hypoplastic kidneys, 1 had hydronephritis, and 1 had a pseudocyst of the kidney. In 1 case in which there was an early equivocal response, the renal lesion was due to obstruction of the renal artery. The presence of hypertension in a child requires thorough investigation, as the etiology may be the secondary type of hypertension and thus curable.

Recurrent Pheochromocytoma: Report of a Case in a Previously Treated Child. T. E. Cane Jr. Pediatrics 21:994-999 (June) 1958 [Springfield, Ill.].

The author describes the clinical course of an 8-year-old boy who was operated on for a recurrent pheochromocytoma of the neck 29 months after the successful surgical removal of the same type of tumor from the right renal area. The patient remained in excellent health after the removal of the original pheochromocytoma and, when he was discharged from the hospital 10 days after the operation, the concentration of catechol amines in the plasma was 8.1 mcg. per liter of arterenol and 0.7 mcg. per liter of epinephrine. The total urinary excretion of catechol amines, determined 5 and 7 days before the second operation, was 1,860 and 2,670 mcg. per 24 hours respectively. The concentration of the catechol amines in the plasma was 13.3 mcg. per liter of circulating arterenol and 1.0 mcg. per liter of epinephrine. These values are above normal. A diagnosis of functionally active pheochromocytoma was made. Two days after operative intervention the concentration of catechol amines in the plasma was 3.8 mcg. per liter of arterenol and 3.2 mcg. per liter of epinephrine.

The tumor was an encapsulated ovoid mass weighing 15 Gm., having the characteristics of a pheochromocytoma, and containing 5 mg. of arterenol per gram of tissue and no significant amount of epinephrine. No previous report of a recurrent pheochromocytoma developing at a different site many months after the successful removal of the primary pheochromocytoma could be found. The return of the concentration of the catechol amines to normal from the abnormally elevated preoperative values after the first operation for removal of a pheochromocytoma would seem to rule out the possibility of an undetected additional tumor at the time of the original operative procedure.

Otitis in Nurslings: Result of BCG Vaccination. N. I. Soboleva. Arkh. pat. 20:67-73 (No. 4) 1958 (In Russian) [Moscow].

The author had observed in a number of nurslings a peculiar type of otitis developing apparently in connection with the administration of BCG vaccine by mouth in liquid form. The otitis was characterized by granulations on the tympanic membrane and a purulent discharge from the ear. Removal of granulations and administration of PAS, Streptocide, and streptomycin brought about recovery. Myringotomy was performed in a few cases in which the condition deteriorated. The postoperative course was uneventful. Microscopic examination of the postoperative specimens suggested a tuberculous process. The granulation tissue and nodes showed a marked tendency toward fibrosis. Bacteria identical with the BCG strain were isolated in some of the cases. These pathological changes in the middle ear were in all probability related to the administration of liquid BCG vaccine by mouth.

Generalized Congenital Analgesia. M. Lamy, R. Garcin, M. L. Jammet and others. Arch. franç. pédiat. 15:433-448 (No. 4) 1958 (In French) [Paris].

Generalized congenital analgesia was discovered in a young child hospitalized for severe lingual ulceration. The ulceration had started when the child was 9 months old, at the time when the first teeth appeared. At the age of 16 months analgesia was generalized and complete. It was not associated with any vegetative, affective, or intellectual reaction to excitation which is normally painful. It was isolated, without any other sensitive disturbance, and without any other neurological disorder. At the age of 26 months a certain sensitivity to pain seemed to appear, especially to pricking and to chilling. Skin biopsy revealed nerve fibers with free terminations. The authors discuss other cases of this peculiar condition which have been reported in the literature often under different names.

DERMATOLOGY

Streptomycin Dermatitis in Nurses. H. T. H. Wilson. Brit. M. J. 1:1378-1382 (June 14) 1958 [London].

A variety of dermatoses, which include pruritus, erythema, eczema, photosensitivity, urticaria, exfoliative dermatitis, and purpura, have been reported in patients treated with streptomycin. Over a period of 8 years, 14 cases of streptomycin dermatitis were seen among the nursing staff of a London hospital, and 2 more were referred from elsewhere. One of the patients was a male nurse, the remainder being female. The sites most often affected were the sides and backs of the fingers, the backs of the hands, the forearms, the elbow flexures, and the face. All cases were patch-tested against a 5% aqueous solution of streptomycin and penicillin (1,000 units per milliliter). Positive patch reactions were elicited in all except the male nurse, who was negative on 2 separate occasions but gave a positive intradermal reaction associated with a flare-up on the affected parts of the face and hands. Generally, once a nurse has acquired a high degree of sensitivity to streptomycin, she (or he) can seldom if ever handle the antibiotic again. One nurse lost her sensitivity 2 years after the initial outbreak, and another nurse showed diminution of sensitivity within 2 to 3 years; the remainder exhibited little, if any, loss of sensitivity during the period of observation unless steps had been taken to desensitize them. Desensitization was attempted in cases where it was not practical for the nurses to actively avoid handling the substance. Six of the nurses were successfully desensitized, with a relapse in one case and a partial relapse in another.

Kaposi's Sarcoma Superimposed on Erythroderma Psoriaticum. A. E. Segal and M. J. Costello. A. M. A. Arch. Dermat. 77:642-647 (June) 1958 [Chicago].

The authors report on an 84-year-old woman with simultaneous occurrence of erythroderma psoriaticum and Kaposi's multiple idiopathic hemorrhagic sarcoma. The patient was admitted to the service of dermatology and syphilology of the Bellevue Hospital Center in New York and was treated for universal erythroderma psoriaticum with hydrocortisone given orally in doses of 80 mg. daily and weekly intramuscular injections of corticotropin (Acthar) gel for 4 months. She then was given prednisone (Meticorten) orally in doses of 20 mg. daily, and treatment was continued indefinitely with a maintenance dose of 15 mg. daily. The psoriasis during this period was characterized by remissions, during which the erythroderma faded and distinct plaques of psoriasis remained. Attacks of intermittent diarrhea and constipation occurred 1 year after admission. Two years after admission and 7 years after the first manifestation of psoriasis, well-circumscribed, reddish-purple nodules, 4 to 8 mm. in diameter, were noticed. These were semihard and tender. The lesions appeared simultaneously on the extensor surfaces of the extremities, the buttocks, the chin, and the left upper-eyelid. A few days later the palms and soles were involved with similar lesions. Two weeks later blood occurred in the stools, and this was followed by constipation and diarrhea of short duration. Enlarged, slightly tender lymph nodes in the left supraclavicular, axillary, and inguinal regions were observed. Biopsy specimens of psoriatic skin from the back and of a nodular lesion from the back clarified the diagnosis of chronic dermatitis of psoriasiform type and of Kaposi's sarcoma respectively.

Aqueous crystalline penicillin G was given in doses of 500,000 units every 8 hours until a total dose of 20 million units was administered. At the termination of this course of treatment the nodular lesions had regressed 20%. A course of potassium arsenite (Fowler's) solution was administered; the patient's general condition became worse, the erythroderma became severe, but no essential change was noted in the nodular lesions. A total dose of 300 r, administered in 3 weekly treatments to 2 nodular lesions on the palm and on the wrist, resulted in complete disappearance of the lesion on the wrist. The patient died, and autopsy was performed. The final anatomic diagnosis was Kaposi's idiopathic hemorrhagic sarcoma with involvement of the skin, pharynx, stomach, small and large intestine, peripancreatic adipose tissue, epicardium, and mammary lymph nodes, thromboembolism of the pulmonary arteries, and chronic ulcers of the stomach. The distribution of the sarcomatous lesions was classic. There was one unique feature, however: the distribution of epicardial and peripancreatic lesions along the course of the medium-sized muscular arteries. This distribution was not noted in the gastrointestinal tract where more of the mucosal distribution was seen. There have been no similar reports in the literature of the simultaneous occurrence of erythroderma psoriaticum and Kaposi's multiple idiopathic hemorrhagic sarcoma in the same patient.

A Case of Fatal Metastasizing "Erythroplasia." M. Witham, M. Garretts, A. Levine and A. Jarrett. Brit. J. Dermat. 70:201-210 (June) 1958 [London].

The case reported is thought to provide a link between the erythroplasia of Queyrat, the plasma-cell type of Zoon, and a sweat-duct carcinoma. Erythroplasia was described by Queyrat in 1911, and it was generally regarded as a precancerous lesion. Darier identified it with Fournier's "epitheliome papillaire nu," pointing out that the surface is brilliant red and velvety and that it develops into an invasive prickle-cell epithelioma; he also mentioned that these lesions are sometimes found on nonmucocutaneous parts of the skin, side by side

with typical Bowen's disease. Zoon in 1950 and 1952 observed cases of erythroplasia characterized histologically by a plasma-cell infiltrate beneath a villous epidermis. He regarded the condition as benign, and so differentiated it from Queyrat's erythroplasia. The authors' patient presented himself with numerous psoriasiform patches of Bowen's disease and 1 large brilliant red plaque resembling erythroplasia. Histologically, one portion of the erythroplasic plaque had the structure of Zoon's type, and another portion showed Bowenoid changes in the epidermis. Later, this plaque became frankly malignant and spread rapidly as "cancer en cuirasse." It also gave rise to copious visceral metastases which proved fatal. Some of these resembled metastases from a breast cancer. Renewed histological studies of the erythroplastic plaque revealed, in the earlier biopsies, evidence of sweat-duct proliferation and, in the later ones, features resembling nevus syringoadenomatosus papilliferus, except that the duct cells had become malignant and filled the lumen. Some of the visceral metastases showed similar features. It is suggested that this is a case of sweat-duct carcinoma with features indicating relationship between nevus syringoadenomatosus papilliferus, Paget's disease, both types of erythroplasia, and some cases of Bowen's disease.

UROLOGY

Primary Amyloidosis of the Ureter. B. F. Andreas and M. Oosting. J. Urol. 79:929-931 (June) 1958 [Baltimore].

Amyloidosis of the genitourinary tract is relatively rare, but several cases involving the bladder have been reported, as well as 1 case involving both the renal pelvis and the ureter. Since the authors were unable to find any previous cases in the American literature involving only the ureter, they report their observations on a 12-year-old girl who had primary amyloidosis of the ureter. The presenting symptoms were pain in the costovertebral angle and hematuria. On surgical exploration the lower third of the ureter was found to be dilated to approximately 1 cm., and the wall of the ureter in this region was markedly thickened and showed what appeared to be a severe inflammatory process. A left-sided ureteronephrectomy was performed; the patient's postoperative course was uneventful. The small, pale kidney weighed 60 Gm. with 15 cm. of ureter attached. The distal portion of the ureter was dilated and thickened, having a waxy, granular appearance, with patches of hemorrhage. The mucosa showed areas of hyperplasia as well as ulceration. Hematoxylin and eosin stains suggested a degenerative process as seen in amyloidosis. Subsequent sections stained with Congo red dye as well as with crystal violet gave the reactions characteristic of amyloid deposition. Two and one-half years later the child was in good health, of normal weight for her age, and free of genitourinary complaints.

Cystic Disease of the Kidney in Infants. J. W. Hooper Jr. J. Urol. 79:917-924 (June) 1958 [Baltimore].

The author presents a clinical classification of cystic disease of the kidney in infants, which is based on a review of the literature. He lists the following types: (1) unilateral multicystic kidney; (2) multilocular cystic kidney; (3) solitary renal cyst; (4) bilateral multicystic kidney; (5) infantile polycystic kidney; (6) adult polycystic kidney found in infancy; and (7) calyceal cyst. He briefly comments on these forms and then presents the histories of 7 patients who were observed during the past 4 years. Two of the 7 infants had unilateral multicystic or polycystic kidney, and 1 had bilateral multicystic kidney. Two cases of congenital-type polycystic kidney are presented, occurring in identical twins, and, finally, an unusual case of calyceal cyst of the kidney and a case of adult polycystic kidney in an infant are presented. Unilateral polycystic or multicystic kidney, large solitary renal cysts of infancy, and multilocular cyst of infancy should be treated by surgery. Bilateral multicystic kidney and bilateral congenital polycystic kidney are incompatible with life. Adult polycystic kidney in infancy is recognized rarely, and the treatment is merely supportive.

The Cytodiagnosis of Prostatic Carcinoma: A Follow-Up Study. I. N. Frank and W. W. Scott. J. Urol. 79:983-988 (June) 1958 [Baltimore].

The authors have been concerned for the past 8½ years with the application of exfoliative cytology to the diagnosis of prostatic carcinoma. During this period, a total of 10,410 slides were examined from 2,445 patients in the age range in which this lesion is most prevalent. The specimens for examination were obtained by prostatic massage in practically every instance. It was the impression of the clinicians that routine massage creates no demonstrable increase in the spread of the disease or over-all morbidity. In fact, a review of cases in which radical perineal prostatectomy was performed on patients from this clinic yielded survival rates which compared favorably with other such series reported. Most of these patients had been subjected to diagnostic prostatic massage prior to surgery and, in many cases, repeated massage. Adequate specimens are most readily obtainable by moderate lateral to medial digital pressure on the prostate, followed by a milking compression down the median furrow to the region of the membranous urethra. An effort is made to avoid the seminal vesicles, since the secretions from these structures dilute and mask

the prostatic material. This technique is no more traumatic than the prostatic massage method used by most urologists in their treatment of chronic prostatitis.

The following are listed as cytological criteria of malignancy: variation in size and shape of nuclei; hyperchromatism; crowding of cells and overlapping of nuclei (in sheets); bizarre, irregular nuclei; chromatin stippling and patches; single large or multiple nucleoli with altered nucleoli-nuclear ratio; mitotic figures (rarely seen); and cast-like cell groupings. Five different classes of cytological smears were differentiated: class 1 was characterized by absence of abnormal or atypical cells; in class 2 smears atypical cells were present but without abnormal features; in class 3 smears there were cells with abnormal features but not sufficiently pathognomonic; in class 4 smears large numbers of pathognomonic cells and cell clusters were found; and in class 5 smears large numbers of conclusive cells and cell clusters existed. Class 3 smears were considered suggestive of cancer, and the smears of classes 4 and 5 as cancer positive.

There were 296 patients with these 3 types of cytological smears, that is, 70 with class 3, 159 with class 4, and 67 with class 5 smears. Carcinoma was definitely demonstrated in 46.7% of those with class 3 smears, in 83.8% of those with class 4 smears, and in 97% of those with class 5 smears. False-positive and false-negative reports are discussed. The authors feel that the prostatic smear does offer a useful adjunct to the diagnosis of prostatic carcinoma. The information obtained from this procedure, used in conjunction with clinical impression, x-ray reports, phosphatase studies, and biopsy, should give maximum accuracy of diagnosis. The authors are presently evaluating the additional determination of the prostatic acid phosphatase, which they consider to be a more accurate and sensitive measure than the total serum acid phosphatase. The specimen for cytological examination may be readily collected at the time of the patient's first visit and repeated as needed. On the average, 2 specimens were obtained by massage per patient in this series.

True Hermaphrodite Siblings. W. A. Milner, W. B. Garlick, A. J. Fink and A. A. Stein. J. Urol. **79**:1003-1009 (June) 1958 [Baltimore].

True hermaphroditism has been defined as the presence in the same individual of both ovarian and testicular tissues. The 68 cases reported probably represent only a small part of the actual incidence. There have been no previous reports on true hermaphroditism in siblings. The authors present 2 "brothers" who were proved to be true hermaphrodites. A 13-year-old boy was admitted to hospital with an undescended left testis. There were 1 older male sibling, aged 17 years, considered to be normal, and a 12-year-old brother and a 5-year-old sister also without genital anomalies. A 1-year-old brother, however, was stated to have a marked chordee, penoscrotal hypospadias, and undescended right testis.

In the 13-year-old boy a small testis was palpable in the left inguinal canal, but it was not possible to bring it down to the scrotum manually. The right testis was in the scrotum, and a pea-sized nodule was palpable on its upper pole. The penis presented a balanitic one-degree hypospadias. A specimen was taken from the lower pole of the left testis for biopsy. The next day, a left-sided orchiopexy and hernia repair with the scrotal placement of a normal-appearing testis and epididymis were performed. Division of the rudimentary chordee was likewise accomplished. A right-sided scrotal exploration then revealed a brown, abnormal-appearing testis, seemingly enclosed in a translucent serous membrane with a normal, loosely attached epididymis. The upper pole of the testis consisted of a firm, rubbery, brown nodule which shelled out easily from its testicular bed. Frozen section revealed a sclerosed testis containing a few small cystic spaces. Permanent sections showed an atrophic sclerosed testis surrounded by dense fibrous tissue which merged into typical ovarian tissue containing multiple graafian follicles. About 18 months later the boy complained of progressive breast enlargement and monthly recurring breast tenderness. Laparotomy and bilateral scrotal explorations were performed. Examination of the pelvis did not reveal any female structures, and each vas deferens to the internal inguinal ring was also normal. The pelvic outlet was androgynoid. The right gonad and spermatic cord were mobilized, and the smooth, ovoid gonad was subjected to bipolar biopsy. The upper pole revealed a focally sclerosed and inflamed epididymis. The inferior pole showed a testis displaying inactive spermatogenesis with moderate interstitial-cell hyperplasia. Attention was then directed to the left gonad, which appeared rudimentary with a thin translucent-like tunica albuginea and slightly nodular in its superior pole. It was felt that the upper pole represented an ovarian segment of an ovotestis. On frozen-section examination, this tissue was again reported as showing inactive spermatogenesis and interstitial-cell hyperplasia. Biopsy of the lower pole revealed ovarian tissue containing numerous ova and some follicular cysts. The left gonad was excised.

In the younger brother the exploration of both testes also revealed ovarian tissue. The association of the combination of hypospadias and cryptorchidism, present in almost all the previously reported

instances of true hermaphroditism, was similarly noted in these 2 siblings. The authors believe that the presence of a testicular nodule combined with an external genital defect should suggest the diagnosis of true hermaphroditism and indicate the need for surgical exploration. Surgical sexual gonadal separation in the majority of ovotestes is feasible and histologically complete. The finding of true hermaphrodite siblings has given indirect support to the geneticists in their controversy concerning the etiology of this condition.

THERAPEUTICS

Clinical and Laboratory Studies with Chlorothiazide: An Oral Diuretic. W. C. Watson, T. J. Thomson and J. M. Buchanan. Lancet 1:1199-1201 (June 7) 1958 [London].

The authors investigated the nature and degree of diuresis obtained with chlorothiazide in various clinical states associated with retention of fluid. Twenty-six "acute" experiments were performed on 22 patients with the following clinical conditions: congestive heart-failure, cor pulmonale with cardiac edema, preeclamptic toxemia of pregnancy, chronic azotemic uremia, nephrosis, hypertension, hepatic cirrhosis with ascites and edema, fulminating bronchiolitis and acute congestive heart-failure, and "steroid" edema. The term "acute" experiment implies the effect of a single oral dose of 2 Gm. of chlorothiazide. The patient's urine was collected for 24 hours up to 9 a. m. on the day of the test. At 9 a. m. he was given 2 Gm. of chlorothiazide, and the next 24 hours' excretion of urine was collected in 2 amounts—a 6-hour fraction and an 18-hour fraction. Each sample of urine was measured, its pH recorded, and its sodium, chloride, and potassium concentration estimated. Samples of blood were taken at the end of each collection period, and their protein, urea, sodium, chloride, potassium, and alkali reserve were estimated.

There was considerable increase in the flow of urine, which is greater in the 6 hours immediately after the administration of chlorothiazide. The diuresis induced by chlorothiazide is associated chiefly with an increased excretion of sodium and chloride. When the serum levels of these electrolytes are low, the drug will not compel their excretion: in such circumstances it tends to promote the excretion of potassium and bicarbonate. Hypochloremia can easily be corrected, however, by administering ammonium chloride, and this simple expedient might augment the diuretic action of chlorothiazide in such patients as it augments the action of mersalyl. In general, the best diuretic response occurred in the type of patient who responds well to mersalyl. In patients with pulmonary heart disease the response was disappointing. After 6 months' experience with chlorothiazide the authors are not certain that tolerance develops; nor are they convinced that a regimen of divided doses (i. e., 10 Gm. twice daily) has any clinical advantages. They feel that, unless there are urgent reasons for obtaining a maximal diuresis, single doses are preferable because they avoid the fatigue of unnecessary nocturia.

Preliminary Report on Clinical and Bacteriological Observations in Treatment of Specific Pulmonary Diseases with Ethereal Oils (Oleum Spicae) in Combination with Streptomycin. A. Liener. Beitr. Klin. Tuberk. 118:148-161 (No. 3) 1958 (In German) [Berlin].

Combination therapy to prevent the development of resistance on the part of the tubercle bacilli against antibiotics was particularly important to Liener, because a large percentage of the patients at his hospital had extensive and old lesions in which long-term antibiotic therapy was necessary. Since the combined use of antibiotics involves the problem of the development of hypersensitivity in the patient, he deemed it advisable to investigate Stickl's observation that the addition of small amounts of ethereal (volatile) oils would greatly increase the bacteriostatic effects of streptomycin. First, in vitro tests were made on tubercle bacilli cultures with streptomycin and the volatile extracts of spike lavender oil (oleum spicae). This volatile oil was used because an injectable preparation of this oil (known as Tavipec) was available. A trial in patients was then begun with a small daily dose of 250 mg. of streptomycin. In addition the patients were given in the morning and in the evening an intramuscular injection of 1 ampule of the preparation of spike oil. Patients with especially severe lesions were given the spike oil also by inhalation. All 51 patients who were subjected to this treatment were kept under strict bacteriological and clinical control, and when there were signs that the process became progressive, the therapy was changed.

The author emphasizes that this is a preliminary report, which aims to induce others to study the combination therapy of streptomycin with volatile oil on larger numbers of patients. In his series the development of resistance to streptomycin was definitely delayed by giving streptomycin in the small dose of 250 mg. daily, together with 2 ampules of the volatile spike oil. The probability that the action of antibiotics is potentiated by the parenteral administration of the volatile extracts of spike oil was greatly increased by the reported observations. The therapeutic results obtained (even admitting the limited number of patients) compared favorably with those obtained with other forms of combination therapy. Further studies will be necessary to ascertain whether optimal effects were

obtained with the dosage used. The method did exert a therapeutic effect. No serious secondary effects were produced with the spike oil.

PATHOLOGY

Carcinoma of the Stomach in Hiroshima, Japan. E. S. Murphy. Am. J. Path. 34:531-542 (May-June) 1958 [Ann Arbor, Mich.].

Carcinoma of the stomach is the most frequent neoplastic disease for both men and women in Japan. In 1955 it was decided that the pathology department of the Atomic Bomb Casualty Commission should undertake an investigation of the occurrence of carcinoma of the stomach in the population of Hiroshima. The aim was to determine any differences in incidence, age of onset, or type of gastric tumor occurring in the population group exposed to mass irradiation as compared with a nonexposed population. A total of 535 patients with carcinoma of the stomach were listed in the surgical and autopsy records of the Hiroshima commission between Dec. 1, 1948, and June 30, 1957. Of these patients, 187 had been exposed to the explosion of the atomic bomb. No significant differences were found between the exposed and the nonexposed groups for the average age at the time of diagnosis, the age distribution in 5-year age groups, the postoperative survival time, or the histological pattern and location of the tumor in the stomach. The incidence of all neoplasms in the exposed and nonexposed groups was also calculated and found to be almost equal. The possibility that the definition of "exposure" was too broad and was thus hiding effects in the patients exposed at 2,500 meters or less was considered, and the material was reexamined with 2,500 meters from the hypocenter as the limit of exposure. The patients exposed at between 2,500 and 10,000 meters were added to the control group. The incidences of carcinoma of the stomach and of all neoplasms were again calculated and again found to be approximately equal. In the patients treated by a surgical resection of the cancer through 1956, a follow-up was possible in 252; 93 of these were still living, but only 7 had lived more than 5 years after the operation. Only 1 of these was an exposed patient, but no significance was attached to this finding.

Bacteriological Studies on Hospitalism and Its Epidemiology with Consideration of Serologic Methods for Differentiation. P. Naumann and W. Heusser. Chirurg 29:193-198 (May) 1958 (In German) [Berlin].

In an attempt at prophylaxis against hospital infections caused particularly by therapy-resistant coagulase-positive strains of staphylococci, the authors carried out bacteriological studies in 7 departments of the surgical clinic of the University in Hamburg, Germany. Smears obtained from wounds of patients, rhinolaryngeal smears obtained from the hospital staff, and the hands of the latter were studied in order to ascertain the various possibilities of transmission along the pathway of the infection. One hundred twenty-four wound smears were obtained from 114 patients, and 47 strains of Staphylococcus pyogenes var. aureus were cultured from the specimens obtained from 46 of these patients. Thus, 46 (about 40%) of these 114 patients were infected by pyogenic staphylococci. Forty-five (about 98%) of the 47 strains of staphylococci were resistant to penicillin. Twenty-three of 34 staff members (10 physicians, 20 nurses, and 4 administrative workers) were carriers of pyogenic staphylococci; of the 37 isolated strains, 30 were obtained from rhinolaryngeal smears of the hospital staff, and 7 were obtained from the hands of these staff members. Thirty-two of the 37 strains were resistant to penicillin. These data corresponded with those obtained by other workers. A study of the dust in the air of 15 hospital wards showed that in 13 of these wards dust particles in the air were infected by pathogenic staphylococci, and of 25 strains cultured, 19 were resistant against penicillin and streptomycin. Bacteriological examination of 30 woolen bed covers revealed pathogenic staphylococci in 3 of these covers. Strains of coagulase-positive staphylococci were obtained from 2 of 24 roentgen-ray films examined for the presence of such bacteria.

Since the behavior of staphylococci against antibiotics does not represent a property which is unchangeable, and since this behavior depends to a great extent on the type of antibiotic preparation employed for treatment, conclusions cannot be drawn from this behavior. Consequently serologic typing of the 114 strains of staphylococci which were obtained by culture was carried out according to the techniques devised by Cogan and Oeding and modified by Grün. Most of the strains belonged to the ABCE, AB, and B antigen groups. The AB strains were definitely identified as so-called hospital bacteria according to their distribution among the hospital staff and their occurrence in the dust particles in the air and in the bed covers as well as because of their frequent occurrence in secondary-infected wounds. Concerning the strains with the ABCE and B antigen structure, it could only be suspected that they had originated from members of the nursing staff. With the aid of sensitivity tests to antibiotics and of serologic methods, the bivalent differentiation of pathogenic staphylococci by several characteristics which do not depend on one another thus has proved itself as an essential expedient in the detection of sources of infections due to the so-called hospital staphylococci and of the path of their spread.

BOOK REVIEWS

Mould Fungi and Bronchial Asthma: A Mycological and Clinical Study. Volume I. By P. J. van der Werff, Head of Amsterdam Clinic for Allergic Diseases, Amsterdam. With foreword by Prof. Dr. Johanna Westerdijk, Director of Centraalbureau voor Schimmelcultures, Baarn, Netherlands. Cloth. $7.50. Pp. 174, with 67 illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; H. E. Stenfert Kroese N. V., Pieterskerkhof 38, Leiden, Holland, 1958.

In the last 25 years or so, the importance and frequency of hay fever and asthma from the airborne spores of molds have been largely investigated by American workers, but before this period the Dutch physician, W. Storm van Leerwen, conducted experiments which pointed to molds as a common cause of asthma. The author of this volume is a disciple of Kremer who was associated with van Leerwen. It is thus particularly appropriate that the most complete presentation on this subject is written by such a man. The book describes climates in relation to mold allergy, gives a survey of general mycology, and gathers the findings from all over the world on the presence of mold spores in the open air, in homes, and in special occupational environments. Ample data are given for the preparation of a variety of culture mediums. There are a large number of photographs of molds. Some are excellent, but many could be improved if they are to serve a teaching purpose. The references are quite complete. The clinical allergic and immunological aspects are reserved for a second volume. This book will interest every one seriously interested in allergy as well as mycology.

High Arterial Pressure. By F. H. Smirk, M.D., F.R.C.P., F.R.A.C.P., Professor of Medicine, University of Otago, Dunedin, New Zealand. Cloth. $15. Pp. 764, with illustrations. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill.; Blackwell Scientific Publications, Ltd., 24-25 Broad St., Oxford, England; Ryerson Press, 299 Queen St., W., Toronto 2B, Canada, 1957.

This book is presented "for consecutive reading and for reference on problems arising in practice." Those sections dealing with the several areas to which the author has made personal contributions are enthusiastically presented and are correspondingly interesting. The concept of essential hypertension as the culmination of a series of repetitive pressor episodes of varied origin accords with most current thinking. Chapters on the incidence and prognosis of hypertension provide useful statistical compendiums. The presentation is extensive but lacks proportion. Even the best sections devote much space to more or less irrelevant details and tend, thereby, towards tedium. Thus, it seems unnecessary to consider the ganglion blockers, including some of dubious marketability or interest, individually in such great detail. Some sections, notably, those removed from the author's direct interests, seem to have been assembled without much attempt at evaluation from a large but not comprehensive bibliography. Certain chapters do not convey as much information as seems desirable. The discussion of arteriosclerosis is sketchy. Consideration of hypertensive encephalopathy focuses on transient cerebral attacks rather than on the ominous syndrome of rising arterial pressure, increasing headache, and progression from stupor to coma. Anticoagulant treatment of cerebrovascular disease is not considered. Pyelonephritis, an important remediable cause of hypertension, is hastily dealt with, with no consideration of the indications for or interpretation of sediment counts, quantitative urine cultures, or urograms. Renal artery lesions are reviewed as causes of hypertension but without discussion of their diagnosis by angiography or other means. The description of aldosteronism conveys no recognizable picture. It would seem arbitrary to list hydralazine under "drugs mostly of academic interest" and premature to suggest that the rauwolfia alkaloids are substantially, rather than quantitatively, different in their psychic effects or that mecamylamine shows little cross tolerance as compared to other ganglion blockers. Most persons will use this as a reference book. Few will be tempted to read it consecutively. As concerns problems of practice, its best function is to provide detailed authoritative information on the treatment of hypertension with ganglion blockers alone or in combination with reserpine and on the organization of a clinic for this purpose. The author is to be commended for his insistence on the need for vigorous maximal control of high arterial pressure in patients with hypertensive disease. His experience justifies this, and the point is not generally appreciated. His comments on the psychic gain experienced by patients whose severe hypertension is brought under control describe an elusive but significant aspect of such treatment.

Advances in Cancer Research. Volume V. Edited by Jesse P. Greenstein and Alexander Haddow. Cloth. $10.80. Pp. 463, with illustrations. Academic Press, Inc., 111 Fifth Ave., New York 3, 1958.

This book should be of interest to experimentalists in several disciplines but will be of little interest to the average clinician except in its discussions of primary cancer of the liver (by Berman, of South Africa) and of tumor-host relations (by Begg, of

These book reviews have been prepared by competent authorities but do not represent the opinions of any medical or other organization unless specifically so stated.

the University of Western Ontario). Other topics discussed are protein synthesis and growth processes, the newer concept of cancer toxin, chemically induced tumors of fowls, anemia in cancer, specific tumor antigens, and the chemistry and carcinogenicity of 2-fluorenamine and related compounds. The international flavor of the volume is indicated by contributions from Russia, England, Japan, Scotland, and the United States. Berman concludes that environmental factors, both cirrhotogenic and carcinogenic, are probably responsible for hepatic neoplasia occurring in a favorably prepared "soil" largely determined on a nutritional basis. Price and Greenfield (of the National Cancer Institute, U. S. Public Health Service) emphasize the inadequacy of understanding of the mechanisms of anemia in the patient with cancer and the need to explore vascular influences in erythrocyte destruction. Tables and figures are few in number. There are no illustrations. Extensive reference lists are appended to each chapter, with an all-inclusive author index. The type is admirably readable.

Methods in Physical Education: An Illustrated Textbook for Students Preparing to Teach Boys and Girls in Secondary Schools. By Hilda Clute Kozman, Ph.D., Rosalind Cassidy, Ed.D., Professor of Physical Education, University of California, Los Angeles, and Chester O. Jackson, Ed.D., Professor of Physical Education, University of Illinois, Urbana. Third edition. Cloth. $6. Pp. 549, with illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1958.

This is the third edition of a textbook for prospective teachers in secondary schools. Its methods and approach are much improved over those of the previous editions. Noteworthy is the greater degree of personalization for the student, with stress on self-direction, self-management, and self-responsibility. Early in the book the authors set their broad goals in terms of frequently quoted requirements for teachers: physical stamina, emotional stability, academic competence, social adaptability, civic capability, communication facility, intellectual versatility, and educative proficiency. On this broad base they build a philosophy of methods and demonstrate how these criteria can be applied to the specific field of physical education. The volume is calculated to broaden the outlook of the prospective teacher through a process of continuing self-appraisal and planning for improvement; yet, with all of its stress on "you, the teacher," and its emphasis on teaching methods and procedures, it does not lose sight of the child who rightfully is held as the central focus in each aspect of the educative process. In the view of the authors, physical education is a means to an end rather than an end in itself. It is one method of educating young people through appealing physical activities. In the educational setting its physical benefits are a concomitant outcome rather than the only goal of the program.

Surgery in Infancy and Childhood: A Handbook for Medical Students and General Practitioners. By Matthew White, M.A., M.B., Ch.B., and Wallace M. Dennison, M.D., F.R.F.P.S., F.R.C.S. Cloth. $9.50. Pp. 444, with 267 illustrations. Williams & Wilkins Company, Mount Royal and Guilford Aves., Baltimore 2; E. & S. Livingstone, Ltd., 16 and 17 Teviot Place, Edinburgh 1, Scotland, 1958.

This book is dedicated to the nursing staff of the Royal Hospital for Sick Children in Glasgow, Scotland. The authors' purpose is to introduce to the senior medical student some of the surgical problems encountered in infancy and childhood. It is not intended as a reference book for pediatric or other surgeons. It is based, primarily, on a series of lectures and demonstrations. It is unfortunate that no bibliography was included. Line drawings, sketches, roentgenograms, and photographs (some in color) are well placed, well chosen, and informative. The subjects considered include surgery in infancy and childhood; preoperative care, anesthesia, and postoperative care; trauma; infection; bone; hemangioma and lymphangioma; the esophagus; the stomach; intestinal obstruction in the newborn infant, abdominal pain in infancy and childhood; intestine, colon, rectum, and anus; the umbilicus; testis and epididymis; hernia and hydrocele; liver and spleen; genitourinary system; the thorax; the head; face, mouth, and jaws; the neck; spine and pelvis; upper limbs, lower limbs, and paralysis in childhood. The succint discussion and supporting sketches on congenital cardiovascular anomalies are particularly commendable. The format and composition of the book are pleasing. This volume should be in the library of nursing schools and accessible to medical students, but it cannot compete with American textbooks on the same subject.

Orthopedic Diseases: Physiology—Pathology—Radiology. By Ernest Aegerter, M.D., Professor of Pathology and Director of Department of Pathology, Temple University Medical Center and School of Medicine, Philadelphia, and John A. Kirkpatrick, Jr., M.D., Radiologist, St. Christopher's Hospital for Children, Philadelphia. Cloth. $12.50. Pp. 602, with 354 illustrations. W. B. Saunders Company, 218 W. Washington Sq., Philadelphia 5; 7 Grape St., Shaftesbury Ave., London, W. C. 2, England, 1958.

This new volume is well written and brings a fresh viewpoint to many of the disease entities that are described. Each of its sections is practically a monograph. The first deals with connective tissue in general and includes a brief chapter on radiology of the skeletal system. Section 2 deals with disturbances in skeletal development. Each disease entity is described in general, then the roentgenographic manifestations, microscopic appearance, and prognosis are given. Section 3 discusses disturbances in the normally formed skeleton in a similar way, and section 4 is concerned with tumors. The book is excellently illustrated, and the authors are to be commended for the superior quality of these reproductions. This book is one of the best reference books on orthopedic diseases that has been published.

QUESTIONS AND ANSWERS

METASTATIC CARCINOMA OF THE RECTUM

To the Editor:—*Please give advice on treatment for metastases in the pelvis from carcinoma of rectum, the primary site in a 55-year-old woman. She had a colostomy 12 years ago, and function since then has been quite good. She has considerable pain in the low part of her back at present which is relieved by therapy with opium derivatives, chlorpromazine hydrochloride, and dextro propoxyphene hydrochloride. The pelvic metastases are minimal according to x-ray findings. The pain seems to be out of proportion to the severity of the metastases.*

G. C. Haskell, M.D., Springfield, Ohio.

Answer.—There is no satisfactory treatment for metastatic carcinoma of the rectum. It seems most unusual to have a carcinoma of the rectum recur after 12 years, and one wonders how the diagnosis of pelvic metastases was established. Reexploration may be indicated to determine the nature and extent of the recurrence of the disease. If the involved area can be identified, then local radiotherapy offers the best possibility of providing some relief, although this is admittedly a limited form of treatment. In the absence of more clinical information, a more detailed reply would be speculative. Generally speaking, however, there are no chemotherapeutic agents that have had an important effect on metastatic carcinoma of the large intestine.

Answer.—It is presumed that the metastases are to the bony pelvis and that the interval since treatment of the primary tumor is 12 years. It would be well to be cautious about the diagnosis and to keep in mind that a new disease may have occurred. Bone marrow studies might aid in the diagnosis. It would be well to use opiates sparingly, since the inquirer mentions that the metastases are minimal and, presumably, the patient's general condition is still good. X-ray therapy might be of help, and chemotherapeutic agents, such as triethylenethiophosphoramide, might be tried empirically. If such palliative treatment is unsuccessful, neurosurgical consultation should be requested.

The answers here published have been prepared by competent authorities. They do not, however, represent the opinions of any medical or other organization unless specifically so stated in the reply. Anonymous communications cannot be answered. Every letter must contain the writer's name and address, but these will be omitted on request.

UNILATERAL TEMPOROMANDIBULAR JOINT PAIN

To the Editor:—*A 30-year-old woman had a gradual onset of pain in the right temporomandibular joint one year ago which has been present ever since, occasionally becoming more severe. The other joint has never been involved, and she has no other symptoms associated with this pain. The pain is aggravated when she opens her mouth widely and sometimes by chewing. She states that sometimes there is swelling around the joint, but this has not been noticed by anyone else. The patient has never had any arthritis or other similar illnesses, and a complete physical examination revealed her to be in good physical condition otherwise. X-ray of the mandible and temporomandibular joint, done two months ago, showed a relaxation of the capsular ligament in both joints. No other abnormalities were noted. Please advise on diagnosis and treatment in this case.*

Ralph E. Thompson, M.D., Lebanon, Ore.

Answer.—It is assumed that the presence of any local disease about the temporomandibular joint has been excluded by adequate physical and roentgenographic examinations. Probably the most common cause of the symptoms complained of by this patient is malocclusion. Careful examination by a dental surgeon is indicated. It is not uncommon that patients who experience symptoms of this sort develop a habitual tic of moving the jaw in a peculiar and abnormal way. This serves to continue the irritation. The patient's jaw should be put at rest. The use of a soft diet, avoidance of opening the jaws widely and, if necessary, a chin sling to restrict motion may be tried.

Answer.—Although unilateral pain in the temporomandibular joint may relate to a number of causes, it will appear that in this instance the patient may be suffering from a muscular spasm. This can be determined by injecting procaine hydrochloride into the masseter muscle to determine if the pain disappears. If this does occur, one may be reasonably sure that the problem is not with the joint per se. By way of therapy, the patient should be advised to exercise the muscle by opening and closing the jaw to its maximum extent while the muscle has been anesthetized. If muscle spasm is her problem, this should bring relief.

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TREATMENT OF PIGMENTED NEVI

To the Editor:—*A 12-year-old patient has a number of pigmented nevi on the face and back. These are becoming more prominent and numerous. What would be the best treatment for facial pigmented nevi, with a cosmetic consideration?*

Donald F. McDonald, M.D., Seattle, Wash.

Answer.—With the child 12 years old, it would be preferable not to attempt to remove these nevi. Unless there are some tumors that are clinically premalignant (flat, black, smooth, and hairless) in areas of present or potential trauma (such as on the feet or under straps) there is little to be gained by eradicating them at this age. Recurrences are common in patients before or during adolescence unless complete excision is performed. If the lesions are eliminated by an elliptical excision and suturing, some scarring is to be expected and this may be greater and more disfiguring than anticipated. If the growths are ignored for the time being, many will become elevated and can then be shaved off even with the skin, and trichloroacetic acid can be applied to the bleeding base without producing scarring. Premalignant lesions can be excised and sutured at this age, since cosmetic results are less important here than considerations of future health and life. Chemical treatment of pigmented nevi is inadvisable, for histopathological study of such tumors is to be commended. All excised or shaved specimens should be subjected to microscopic examination. If junctional changes are found in lesions removed ultraconservatively (as by shaving), total postoperative excision should be considered. However, the presence of such alterations in the microscopic section is of less significance in the adolescent than it is in the mature person.

HERPES PROGENITALIS

To the Editor:—*What is the significance of the appearance of herpes simplex on the prepuce of an apparently healthy man, aged 45, and what, if any, treatment should be instituted? The herpes appears every three to four months, mostly on the right side, and seems not to have any connection to sexual activity.*

F. W. Gebhardt, M.D., Dupo, Ill.

Answer.—Herpes simplex occurring on the prepuce, commonly called herpes progenitalis, is caused by irritation or inflammation of the peripheral nerves or ganglionic centers which is induced by various agents. These agents may be local, as the accumulation of smegma. Bouts of mild inflammation may recur from a specific or nonspecific infection of Cowper's gland, the prostate, or any structure in the lower intestine. This reaction may be caused by bacterial agents or by certain foods. The condition in itself is not of major significance, but due to the production of breaks in the skin barrier it may provide a portal of entrance for a more significant infection. The methods of treatment are many, which is always evidence of a lack of having a specific. At the first signs of irritation local applications of hot compresses or immersion of the organ in hot boric acid solutions, followed by topical application of camphor in any of its usual forms, may be abortive. Injections of gamma globulin may hasten the disappearance of a developed lesion. Repeated smallpox vaccinations may also be used, both for prophylaxis and for treatment of the developed lesion. For the infected lesions tetracycline and vitamin B_{12} are useful. Benzoin tincture and the use of x-ray have been recommended. Circumsion may be recommended in certain cases.

PROGESTERONE AND ABORTION

To the Editor:—*Does progesterone have any adverse effect on the fetus in the case of a threatened abortion? If so, would such effect be temporary or permanent?*

Dale C. Hager, M.D., Beaumont, Texas.

Answer.—For many years progesterone has been known to have androgenic properties. Recent reports (Nellhaus, *New England J. Med.* 258:935, 1958; Jones, *Obst. & Gynec. Surv.* 12:433, 1957; Wilkins and Jones, *Obst. & Gynec.* 11:355, 1958) suggest that in the human being masculinization of the female fetus, with production of female pseudohermaphroditism, may be a direct result of the administration of progestational substances to the mother during pregnancy. Ideally, progesterone or allied hormones should be administered during pregnancy only in physiological amounts and only when there is demonstrated deficiency. But, since assay of these substances is not feasible in routine clinical practice, one is forced either to abandon progesterone therapy altogether in cases of threatened and habitual abortion, despite its probable usefulness in some cases, or to decide on a dose which may be helpful but is probably insufficient to cause masculinization if the fetus is a female. It is estimated that through the third month of pregnancy the endogenous production of progesterone averages from 30 to 50 mg. per 24 hours. An appropriate, and probably safe, dose would be of the order of 25 mg. daily or 50 mg. three times a week. In the present state of knowledge, the use of larger doses appears to be contraindicated. With respect to the permanency of this affection, data are as yet too meager to permit conclusion.

EFFECT OF VIBRATION ON PREGNANCY

To the Editor:—*A 39-year-old woman has been married eight years and has no living children. One previous pregnancy, in 1954, resulted in spontaneous abortion. After vigorous infertility treatment, another pregnancy of approximately eight weeks' duration now exists. Threatened abortion has been evident for a good portion of this time, but, with appropriate treatment, her condition now seems stabilized. There are considerable emotional problems, and insomnia is present. A vibrating bed seems to lull her to restful sleep. Is there any possible threat to pregnancy at any stage by the use of such vibration?*

Charles G. Freundlich, M.D., Houston, Texas.

Answer.—As far as is known there is no information available concerning the threat of vibration to pregnancy. Extremely mild vibrations probably have no ill-effects on gestation.

CLIMATE AND EMPHYSEMA

To the Editor:—*A patient, aged 55, has severe and disabling emphysema and bronchiectasis. How much benefit would he obtain by moving to an area with a drier climate, such as Arizona?*

M. W. Hook, M.D., Cheraw, S. C.

Answer.—Patients sometime benefit greatly by a change of climate, particularly if emphysema is related to asthma and if change of environment permits escape from exposure to allergens. On the other hand, some patients suffer from atmospheric dust in an arid climate and others become worse for no apparent reason. A patient should not be encouraged to make a great financial sacrifice to change climate unless a trial period of residence convinces him personally that the change is beneficial.

YEAST IN URINE

To the Editor:—*I would like to take exception to the statement made in answer in a question pertaining to the significance of the finding of yeast organisms in the urine* (J. A. M. A. 167:142, *[May 3] 1958). On many occasions yeast organisms may be seen to produce violent irritation and inflammation with resultant pyuria, dysuria, and symptoms of severe urinary disorder. The finding of yeast organisms in the urine has become magnified many fold during the past few years. Twenty-five or 30 years ago this finding was limited entirely to patients who had diabetes and in whom these organisms apparently had been introduced from without by catheterization or cystoscopic examination or by surgical and other procedures. With the advent of antibiotics and their effect in suppressing the organisms which apparently inhibit yeast growths, an increasing incidence of urinary tract infection has been observed in patients in whom the only organism that could be cultured or found on direct smear was that of yeast or various types of fungous formation. That these are not pathogenic is incorrect; in the practice of myself and my associates in the past few years no less than a dozen intractable infections were seen to be associated solely with yeast. Elimination of the yeast by modern methods, which has been extremely difficult, resulted in the clearing up of the urinary tract infection symptoms and a cure of the inflammatory reaction in the bladder and urethra. The widespread use of antibiotics apparently is giving the yeast an opportunity to become not only more prevalent but also more pathogenic. Whereas formerly only an occasional patient with monilial infection of the vagina would be seen for treatment, of the women who now come for treatment of urologic disorders fully 15 or 20% have either an asymptomatic yeast infection or one which is producing irritative symptoms. About 30 years ago a case of persistent urinary infection associated with the finding of yeast in the urine was so rare that it became the occasion for publication. At the present time, patients found with urinary tract infections, who have been treated with various antibiotics, finally have an infection with yeast and no other organism, and the yeast is more resistant to treatment than any of the bacilli or cocci.*

Vincent J. O'Conor, M.D.
720 N. Michigan Ave.
Chicago 11.

The above comment was referred to the consultant who answered the original query, and his reply follows.—Ed.

To the Editor:—*This consultant agrees that patients are prone to urinary complications due to the use and abuse of antibiotics. However, the question was answered merely on the basis of yeast cells in the patient's urine. No mention was made of the patient having received antibiotics, nor was there mention of whether the urine specimen examined was obtained by catheterization. It is heartily agreed that patients are seen with monilial infections as the result of antibiotic therapy in urinary tract infections. It is the custom in one particular hospital not to use any antibiotic for more than three days and only when it is indicated after a proper culture has been made and sensitivity studies done.*

GUIDES TO THE EVALUATION OF PERMANENT IMPAIRMENT

THE VISUAL SYSTEM

The Committee on Medical Rating of Physical Impairment

PREFACE

Evaluation or rating of permanent disability has long been recognized as an important and complex subject. In the past much confusion has resulted from inadequate understanding by physicians and others of (*a*) the scope of medical responsibility in evaluation of permanent disability; and (*b*) the difference between "permanent disability" and "permanent impairment."

It is vitally important for every physician to be aware of his proper role in the evaluation of permanent disability under any private or public program for the disabled. It is equally important for him to have the necessary authoritative material to assist him in competently fulfilling his particular responsibility—the evaluation of permanent impairment. It is the purpose of this and other reports by the Committee on Medical Rating of Physical Impairment to correct a past confusion of terms and to provide a series of practical guides to the evaluation of various types of permanent impairments.

The following explanations of generally used terms in programs for the disabled will suffice for all practical purposes:

1. *Permanent Disability.*—This is not a purely medical condition. A patient is "permanently disabled" or "under a permanent disability" when his actual or presumed ability to engage in gainful activity is reduced or absent because of "impairment" and no fundamental or marked change in the future can be expected.

2. *Permanent Impairment.*—This is a purely medical condition. Permanent impairment is any anatomic or functional abnormality or loss after maximal medical rehabilitation has been achieved and which abnormality or loss the physician considers stable or nonprogressive at the time evaluation is made. It is always a basic consideration in evaluation of permanent disability. It should be remembered, however, that permanent impairment is a contributing factor to, but not necessarily an indication of, the extent of a patient's permanent disability.

3. *Evaluation (Rating) of Permanent Disability.*—This is an administrative, not medical, responsibility and function. Evaluation of permanent disability is an appraisal of the patient's present and probable future ability to engage in gainful activity as it is affected by nonmedical factors, such as age, sex, education, and economic and social environment, and the medical factor—permanent impairment. Nonmedical factors have proved extremely difficult to measure. For this reason permanent impairment is, in fact, the sole or real criterion of permanent disability far more often than is readily acknowledged. A determination of permanent disability is an administrative decision as to the patient's entitlement.

4. *Evaluation (Rating) of Permanent Impairment.*—This is a function which physicians alone are competent to perform. Evaluation of permanent impairment defines the scope of medical responsibility and therefore represents the physician's role in the evaluation of permanent disability. Evaluation of permanent impairment is an appraisal of the nature and extent of the patient's illness or injury as it affects his personal efficiency in the activities of daily living. These activities are self-care, communication, normal living postures, ambulation, elevation, traveling, and nonspecialized hand activities. It is not and never can be the duty of physicians to evaluate the social and economic effects of permanent impairment. These effects must be evaluated by administrators in making determinations of permanent disability.

Competent evaluation of permanent impairment requires adequate and complete medical examination, accurate objective measurement of function, and avoidance of subjective impressions and nonmedical factors, such as the patient's age, sex, or employability.

The Committee on Medical Rating of Physical Impairment believes that permanent impairment cannot vary because of the circumstances of its occurrence or the geographical location of the patient at the time. Furthermore, unlike disability, permanent impairment can be measured with a reasonable degree of accuracy and uniformity on

Members of the Committee on Medical Rating of Physical Impairment are Drs. Raymond M. McKeown, Chairman, Coos Bay, Ore.; George F. Gsell, Wichita, Kan.; Henry H. Kessler, Newark, N. J.; Quentin W. Mack, Boise, Idaho; James R. McVay, Kansas City, Mo.; and O. A. Sander, Milwaukee. Staff members are Mr. George W. Cooley, Secretary, Chicago; and Mrs. Marjorie W. Grigsby, Research Associate, Chicago.

Consultants in the preparation of this guide were Drs. Ralph W. Danielson, Denver; Charles E. Jaeckle, East Orange, N. J.; and Harold G. Scheie, Philadelphia.

the basis of impaired function as evidenced by loss of structural integrity, pathology, or pain substantiated by clinical findings.

The Committee is familiar with the various formulas developed in the past for use in evaluation of permanent disability. These formulas are usually administrative devices which equate specific medical criteria to specific percentages of permanent partial or total disability (loss of working or earning capacity). From the medical standpoint the medical criteria may undeniably represent various anatomic or functional impairments. However, it is unrealistic to presume that many of these impairments, especially those of a minor nature, will necessarily at some time result in disability. These administrative devices are not generally available to physicians and in any event would not be useful in making sound evaluations of permanent impairment.

On the other hand, although a number of valuable contributions have been made in the past, the Committee found no comprehensive practical system of the type necessary for the evaluation of permanent impairment by individual body systems or of the whole man. For this reason the Committee has undertaken to prepare a series of guides. The Committee has been greatly assisted in its work by the outstanding consultants whose names appear in connection with the appropriate guides.

Two guides are now available: the first, dealing with the extremities and back, was published as a special edition of the Feb. 15, 1958, issue of THE JOURNAL, and the second, concerned with the visual system, is introduced here.

Both guides have been developed after careful study of the literature and of the views of recognized authorities and will be reviewed periodically to insure their continuing value as advances in medical knowledge and technique occur.

Each guide contains recommended percentage values related to the criteria provided. The use of numerical values is preferred because of difficulty in communication and variability in interpretation of such terms as "slight," "marked," and "moderate." Such values provide a practical means of expressing and calculating the extent of permanent impairment and encourage accurate, equitable, and uniform evaluation.

Methods of calculating impairment are uniform, explained in detail with examples, and require a minimum of computation.

Generally, when a single impairment is involved the percentage value may be read directly from the text or transposed to a relative value of a unit of the body or of the whole man by referring to appropriate tables.

When two or more impairments are involved, however, the value of each impairment must be ascertained and transposed to a common denominator, such as the whole man. Thereafter these values must be combined. A combined values table is provided by which any combination of impairments may be easily found. The method generally employed to combine various impairments is based on the principle that each impairment acts not on the whole part but on the portion which remains after the preceding impairment has acted. For purposes of computation, the source and chronology of the impairment values is immaterial.

After the values of all impairments involved have been computed and transposed to a common denominator, the final impairment value, whether the result of single or combined impairments, is expressed in terms of the nearest 5%.

THE VISUAL SYSTEM

Introduction

The purpose of this guide is to provide physicians with criteria for use in evaluating permanent impairment of the visual system. It is adapted from a report prepared by a committee of the Council on Industrial Health in 1955 and entitled "Estimation of Loss of Visual Efficiency." That and previous reports of the American Medical Association have been the basis for rating under numerous programs for the disabled.

The visual system consists of the eyes, adnexa oculi, and the optic pathways. This guide seeks to provide a simplified method for determining permanent visual impairment and its effect on an individual's ability to perform the activities of daily living. Diminished visual ability is expressed as a percentage of impairment of the visual system. Diminished ability of the individual is expressed as a percentage of impairment of the "whole man."

Visual impairment in varying degrees occurs in the presence of a deviation from normal in one or more functions of the eye, including (1) corrected visual acuity for distance and near, (2) visual fields, and (3) ocular motility with absence of diplopia. Evaluation of visual impairment is based on these three functions. Although they are not all equally important, vision is imperfect without the coordinated function of all three.

Other ocular functions and disturbances are considered to the extent that they are reflected in one or more of the three coordinated functions. Such ocular functions include color perception, adaptation to light and dark, accommodation, and binocular vision. Such ocular disturbances include paresis of accommodation, iridoplegia, metamorphopsia, entropion, ectropion, epiphora, and lagophthalmos. To the extent that any ocular disturbance causes impairment not reflected in visual acuity, visual fields, or ocular motility without diplopia, it must be evaluated by the physician as to the degree of impairment and be combined with the impairment of the visual system as determined in the calculations which follow. In such circumstances the physician will be guided by the value relative to the

measurable functions on which evaluation is based in this guide, as well as by the value assigned to other ocular impairments in the individual case. Deformities of the orbit and cosmetic defects which do not alter ocular function are not considered.

The following equipment is necessary to test the functions of the eyes:

1. Visual acuity test charts for (*a*) distance: for purposes of standardization the Snellen test chart with block letters or numbers, the illiterate E chart, or Landolt's broken-ring chart are desirable; (*b*) near: there are many such charts available, using a similar Snellen notation for inches or Jaeger print or point type notation.
2. A standard perimeter with radius of 330 mm. and a tangent screen.
3. Refraction equipment.

Criteria and Methods for Evaluation

Central Visual Acuity.—Illumination of the test chart should be at least 5 foot-candles (f.-c.), and the chart or reflecting surface should not be dirty or discolored from age. The test distances should be 20 ft. (6 m.) for distance and 14 in. (36 cm.) for near vision.

Central vision should be measured and recorded for distance and near with and without correction. The use of contact lenses might further improve vision reduced by irregular astigmatism from corneal injury or disease. However, the practical difficulties of fitting and expense and tolerance of such lenses, in addition to the fact that they are often medically contraindicated, are sufficiently important at present to recommend that only regular ophthalmic lenses be used to obtain the best corrected vision.

Visual acuity for distance should be recorded in the notation of a fraction in which (1) the "numerator" is the test distance in feet or meters; and (2) the "denominator" is the distance at which the smallest letter discriminated by the patient would subtend 5 minutes of arc (the distance at which an eye with 20/20 vision would see that letter).

This fractional designation is purely a convenient form of notation and does not imply percentage of visual acuity. A similar Snellen notation with use of inches or a comparable Jaeger or point-type notation may be used in designating visual acuity for near.

The visual acuity notations for distance and near with corresponding percentages of loss of central vision which appear in table 1 are included solely to indicate the basic values used in developing table 2.

Simple addition of two percentages of loss corresponding to appropriate notations for distance and near does not provide the true percentage loss of central vision. In accordance with accepted principles, true loss of central vision is the mean of the two percentages (table 2).

Monocular aphakia is considered an additional visual handicap and, if present, is assigned a value of 50% decrease in the remaining corrected central vision (table 2).

To Determine Loss of Central Vision in One Eye:

1. Measure and record central visual acuity for distance and near with and without corrective lenses.
2. Consult table 2 for corresponding loss of central vision depending on the presence of monocular aphakia.

TABLE 1.—*Central Visual Acuity Notations*

Distance		
Snellen		*Loss of Central*
English	*Metric*	*Vision, %*
20/16	6/5	0
20/20	6/6	0
20/25	6/7.5	5
20/32	6/10	10
20/40	6/12	15
20/50	6/15	25
20/64	6/20	35
20/80	6/24	40
20/100	6/30	50
20/125	6/38	60
20/160	6/48	70
20/200	6/60	80
20/300	6/90	85
20/400	6/120	90
20/800	6/240	95

Near			
Snellen	*Jaeger*	*Point*	*Loss of Central Vision, %*
14/14	1-	3	0
14/18	2-	4	0
14/22	...	5	5
14/28	3	6	10
14/35	6	8	50
14/45	7-	9+	60
14/56	8	12	80
14/70	11	14	85
14/87	...	...	90
14/112	14	22	95
14/140	...	...	98

EXAMPLE.—Without allowance for monocular aphakia: 14/56 for near and 20/200 for distance produces 80% loss of central vision. With allowance for monocular aphakia (applicable to corrected vision only): 14/56 for near and 20/200 for distance produces 90% loss of central vision.

Visual Fields.—The extent of the visual field is determined by use of the usual perimetric methods with a white target which subtends a 0.5-degree angle (a 3-mm. white disk at a distance of 330 mm.) under illumination of not less than 7 f.-c. A 6/330 white disk should be used for aphakia. The

TABLE 2.—*Loss of Central Vision*[*]

Snellen Rating for *Distance*	Snellen Rating for *Near*										
	14/14	14/18	14/22	14/28	14/35	14/45	14/56	14/70	14/87	14/112	14/140
20/16	0	0	3	5	25	30	40	43	45	48	49
	50	50	52	53	63	65	70	72	73	74	75
20/20	0	0	3	5	25	30	40	43	45	48	49
	50	50	52	53	63	65	70	72	73	74	75
20/25	3	3	5	8	28	33	43	45	48	50	52
	52	52	53	54	64	67	72	73	74	75	76
20/32	5	5	8	10	30	35	45	48	50	53	54
	53	53	54	55	65	68	73	74	75	77	77
20/40	8	8	10	13	33	38	48	50	53	55	57
	54	54	55	57	67	69	74	75	77	78	79
20/50	13	13	15	18	38	43	53	55	58	60	62
	57	57	58	59	69	72	77	78	79	80	81
20/64	18	18	20	23	43	48	58	60	63	65	67
	59	59	60	62	72	74	79	80	82	83	84
20/80	20	20	23	25	45	50	60	63	65	68	69
	60	60	62	63	73	75	80	82	83	84	85
20/100	25	25	28	30	50	55	65	68	70	73	74
	63	63	64	65	75	78	83	84	85	87	87
20/125	30	30	33	35	55	60	70	73	75	78	79
	65	65	67	68	78	80	85	87	88	89	90
20/160	35	35	38	40	60	65	75	78	80	83	84
	68	68	69	70	80	83	89	89	90	91	92
20/200	40	40	43	45	65	70	80	83	85	88	89
	70	70	72	73	83	85	90	91	93	94	95
20/300	43	43	45	48	68	73	83	85	88	90	92
	72	72	73	74	84	87	91	93	94	95	96
20/400	45	45	48	50	70	75	85	88	90	93	94
	73	73	74	75	85	88	93	94	95	97	97
20/800	48	48	50	53	73	78	88	90	93	95	97
	74	74	75	77	87	89	94	95	97	98	99

[*] Upper figure=% loss of central vision without allowance for monocular aphakia; lower figure=% loss of central vision with allowance for monocular aphakia.

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test object is brought from the periphery to the seeing area. At least two peripheral fields should be obtained which agree within 15 degrees in each meridian. The reliability of the patient's responses should be noted. The result is plotted on an ordinary visual field chart on each of the eight 45-degree principal meridians (fig. 1).

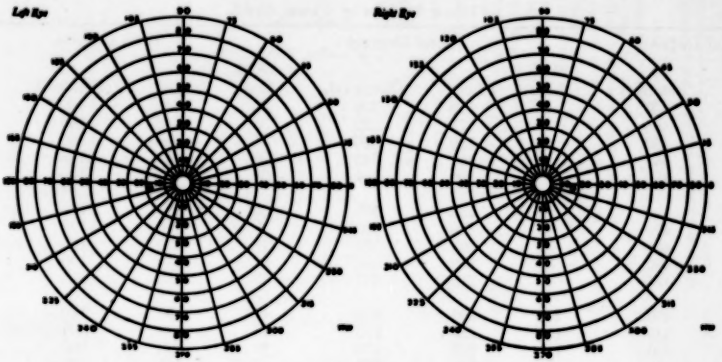

Figure 1

The minimum normal extent of the visual field from the point of fixation is indicated in table 3.

These figures are somewhat less than the average normal, thus allowing for poor or delayed subjective responses or unusual prominence of brow or nose.

TABLE 3.—*Minimal Normal Extent of Visual Field from Point of Fixation*

	Degrees
Temporally	85
Down temporally	85
Down	65
Down nasally	50
Nasally	60
Up nasally	55
Up	45
Up temporally	55
Total	500

The percentage of retained visual field in one eye is obtained by adding the number of degrees of the eight principal meridians given in table 3 for the 3/330 white isopter, which normally is 500 degrees, and dividing by five. Conversely, the percentage loss of visual field is obtained by adding the degrees lost (as measured from the norms in table 3) in each of the eight principal meridians and dividing the total by five. Where there is a loss of a quadrant or a half field, it is necessary to add the total of the loss in each meridian to half the sum of the two boundary meridians. Visual field loss can be calculated for other defects in a similar manner.

Although the extent of visual field loss cannot be determined accurately for scotomas, an approximation can be obtained by subtracting the width of the scotoma from the peripheral visual field value at those same meridians. A similar estimation of visual field loss can be applied to enlargement of the blind spot with use of a 2-mm. test object at a distance of 1 m. from a tangent screen with the patient wearing his corrective lenses. For example, a general enlargement of the blind spot of 5 degrees would result in a visual field loss of $8 \times 5 \div 5 = 8\%$ loss. Because a central scotoma directly affects the central visual acuity, which is first evaluated, such visual field loss is not again used in the final calculation of visual loss.

To Determine Loss of Visual Field:

1. Plot the extent of visual fields in each of the eight 45-degree meridians on an ordinary visual field chart (fig. 1).

2. (*a*) Determine the degrees lost by adding the degrees of visual field lost in each of the principal meridians (table 3).

EXAMPLE.—A concentric contraction to 30 degrees.

Loss	Degrees
Temporally	55
Down temporally	55
Down	35
Down nasally	20
Nasally	30
Up nasally	25
Up	15
Up temporally	25
Total loss	260

TABLE 4.—*Loss of Visual Field*

Total Degrees			Total Degrees			Total Degrees		
Lost	Retained	% of Loss	Lost	Retained	% of Loss	Lost	Retained	% of Loss
0	500*	0	170	330	34	340	160	68
5	495	1	175	325	35	345	155	69
10	490	2	180	320	36	350	150	70
15	485	3	185	315	37	355	145	71
20	480	4	190	310	38	360	140	72
25	475	5	195	305	39	365	135	73
30	470	6	200	300	40	370	130	74
35	465	7	205	295	41	375	125	75
40	460	8	210	290	42	380	120	76
45	455	9	215	285	43	385	115	77
50	450	10	220	280	44	390	110	78
55	445	11	225	275	45	395	105	79
60	440	12	230	270	46	400	100	80
65	435	13	235	265	47	405	95	81
70	430	14	240	260	48	410	90	82
75	425	15	245	255	49	415	85	83
80	420	16	250	250	50	420	80	84
85	415	17	255	245	51	425	75	85
90	410	18	260	240	52	430	70	86
95	405	19	265	235	53	435	65	87
100	400	20	270	230	54	440	60	88
105	395	21	275	225	55	445	55	89
110	390	22	280	220	56	450	50	90
115	385	23	285	215	57	455	45	91
120	380	24	290	210	58	460	40	92
125	375	25	295	205	59	465	35	93
130	370	26	300	200	60	470	30	94
135	365	27	305	195	61	475	25	95
140	360	28	310	190	62	480	20	96
145	355	29	315	185	63	485	15	97
150	350	30	320	180	64	490	10	98
155	345	31	325	175	65	495	5	99
160	340	32	330	170	66	500	0	100
165	335	33	335	165	67			

*Or more.

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(*b*) If a half field is lost, add the degrees lost to half the sum of the two boundary meridians.

EXAMPLE.—Entire temporal field lost.

Loss	Degrees
Up temporally	85
Temporally	85
Down temporally	55
Av. of up and down	55
Total loss	280

3. Consult table 4 to ascertain corresponding percentage loss of visual field.

EXAMPLE.—Total loss of 280 degrees=52% loss of visual field.

Ocular Motility.—Unless diplopia is present within 30 degrees of the center of fixation, it rarely causes significant visual loss except on looking downward. The extent of the diplopia in the various directions of gaze is determined on the perimeter at 330 mm. or on any tangent screen at a distance of 1 m. from the patient in each of the 45-degree meridians, with use of a small test light and without the addition of colored lenses or correcting prisms.

To Determine Loss of Ocular Motility in One Eye:

1. Plot the results of the separation of two images on a visual field chart.

2. Add the corresponding percentage loss of ocular motility caused by diplopia in various positions of gaze as given in figure 2 below.

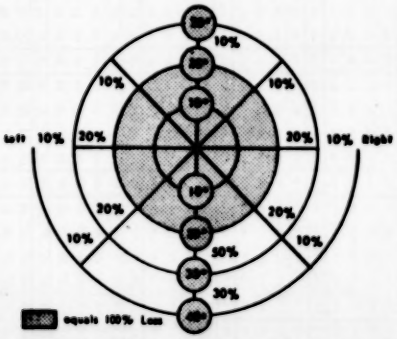

Fig. 2.—Percentage loss of ocular motility of one eye in diplopia fields.

EXAMPLE.—Diplopia within the central 20 degrees=100% loss of ocular motility.

EXAMPLE.—Diplopia on looking to the side from 20 to 30 degrees=20% loss of ocular motility
30 to 40 degrees=10% loss of ocular motility
30% loss of ocular motility

To Determine Impairment of the Visual System:

1. Calculate separately and record for each eye.
   (*a*) percentage loss of central vision (CV)
   (*b*) percentage loss of visual field (VF)
   (*c*) percentage loss of ocular motility (OM)

2. Using combined values table, combine percentage loss of central vision with percentage loss of visual field in each eye separately. Record these values.

EXAMPLE.—Right eye—
loss of central vision 56%
loss of visual field 32%
(56 combined with 32=70) 70%
Left eye—
loss of central vision 46%
loss of visual field 32%
(42 combined with 32=63) 63%

3. Again using the combined values table, combine percentage loss of ocular motility in eye with greatest loss with combined value for central vision and visual field in that eye. Disregard loss of ocular motility in other eye.

EXAMPLE.—Right eye—
combined value of CV and VF 70%
loss of ocular motility 25%
(70 combined with 25=78) 78%

4. Consult table 5 to ascertain impairment of the visual system.

EXAMPLE.—Impairment of
right (worse) eye 78%
Impairment of
left (better) eye 63%
Impairment of visual system 67%

EXAMPLE.—Impairment of
right (worse) eye 90–100%
Impairment of
left (better) eye 0%
Impairment of visual system 25%

NOTE.—Binocular aphakia is considered an additional visual handicap of 25% if evaluation has been based on corrected central vision. If, however, uncorrected central vision has been used in evaluation, allowance for aphakia has already been made.

5. Consult table 6 to ascertain impairment of whole man contributed by impairment of visual system.

EXAMPLE.—67% impairment of visual system=63% impairment of whole man.

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TABLE 5—VISUAL SYSTEM *

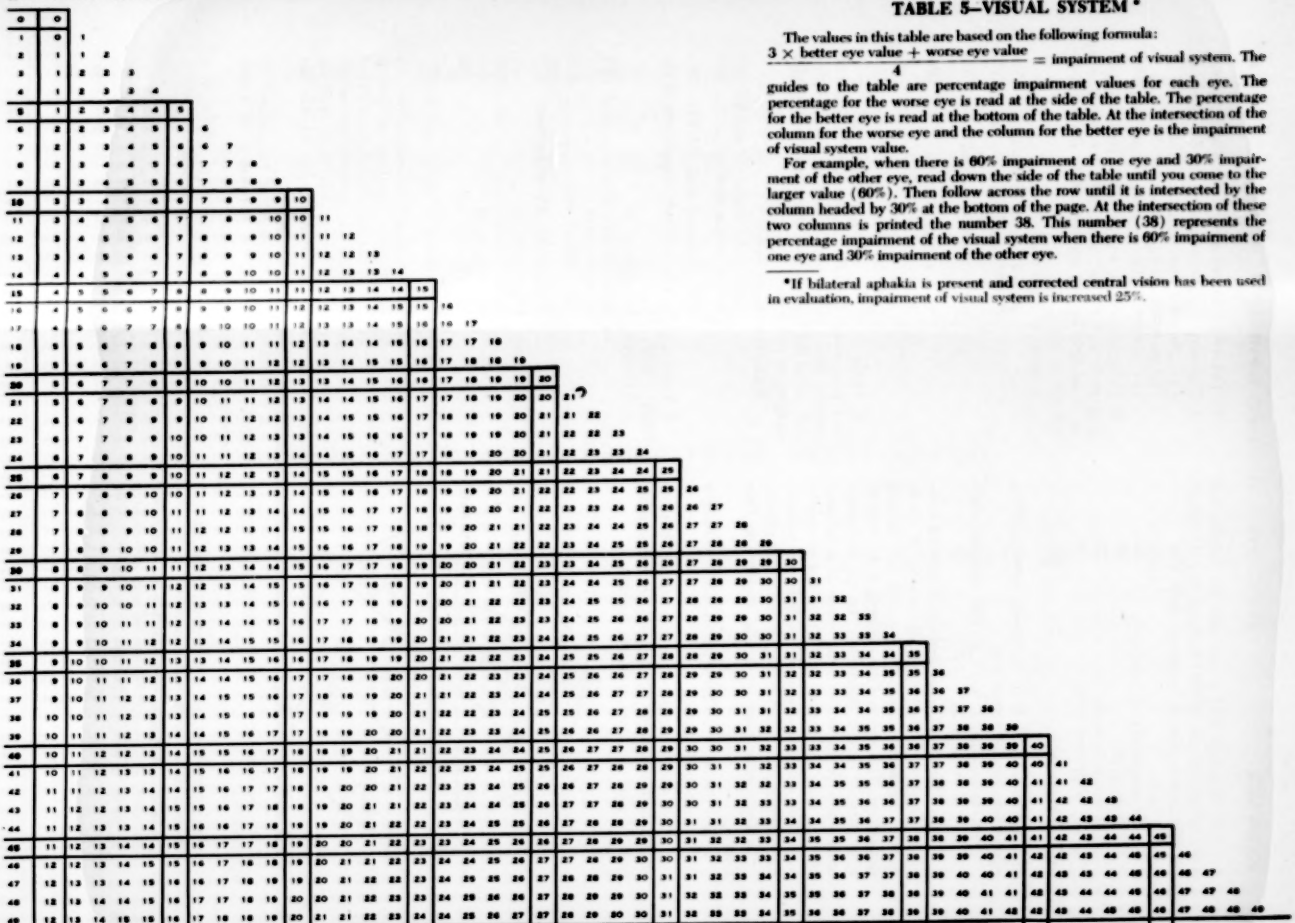
The values in this table are based on the following formula:

$$\frac{3 \times \text{better eye value} + \text{worse eye value}}{4} = \text{impairment of visual system.}$$

The guides to the table are percentage impairment values for each eye. The percentage for the worse eye is read at the side of the table. The percentage for the better eye is read at the bottom of the table. At the intersection of the column for the worse eye and the column for the better eye is the impairment of visual system value.

For example, when there is 60% impairment of one eye and 30% impairment of the other eye, read down the side of the table until you come to the larger value (60%). Then follow across the row until it is intersected by the column headed by 30% at the bottom of the page. At the intersection of these two columns is printed the number 38. This number (38) represents the percentage impairment of the visual system when there is 60% impairment of one eye and 30% impairment of the other eye.

*If bilateral aphakia is present and corrected central vision has been used in evaluation, impairment of visual system is increased 25%.



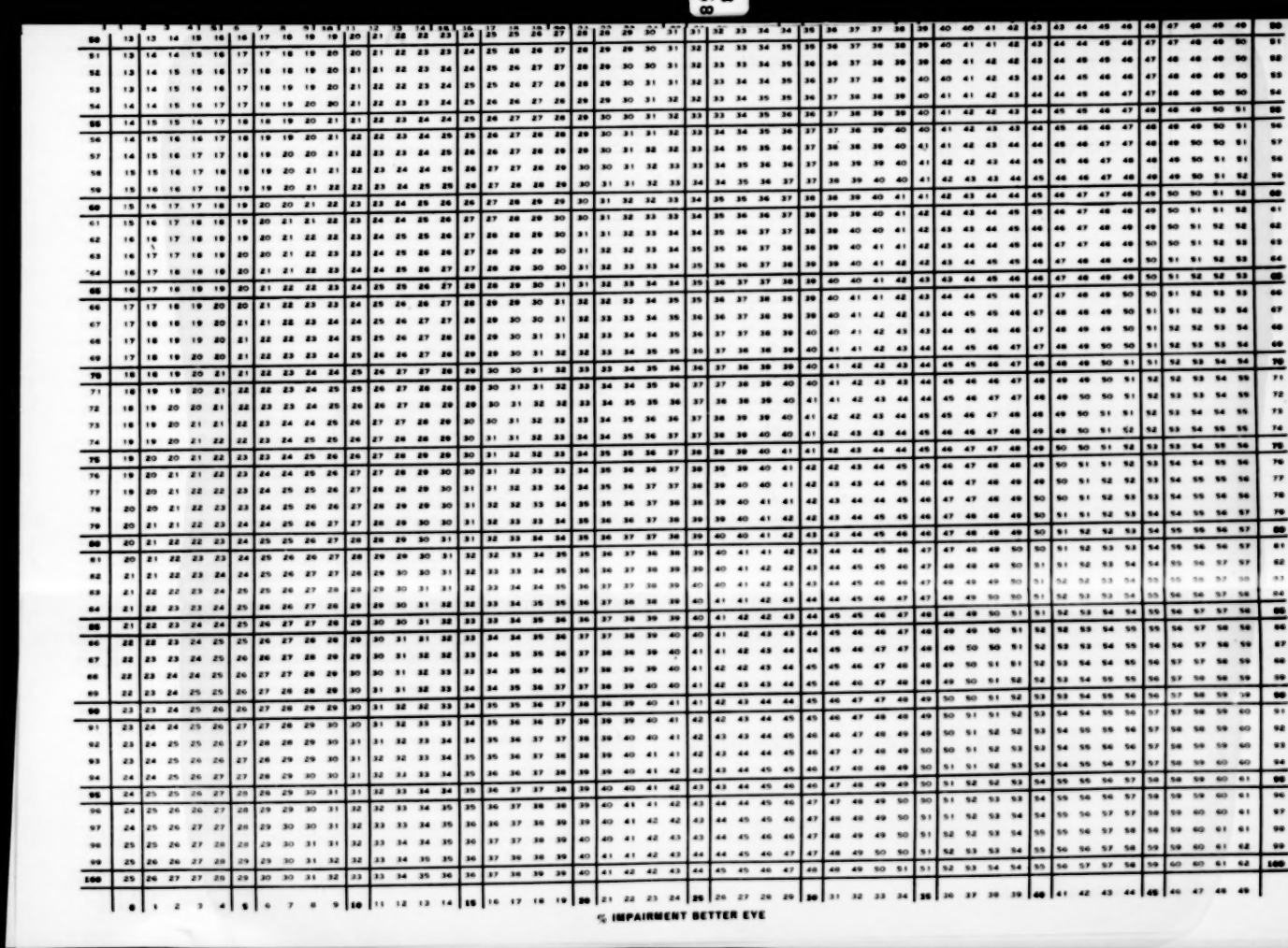

% IMPAIRMENT BETTER EYE

TABLE 5 (CONTINUED)

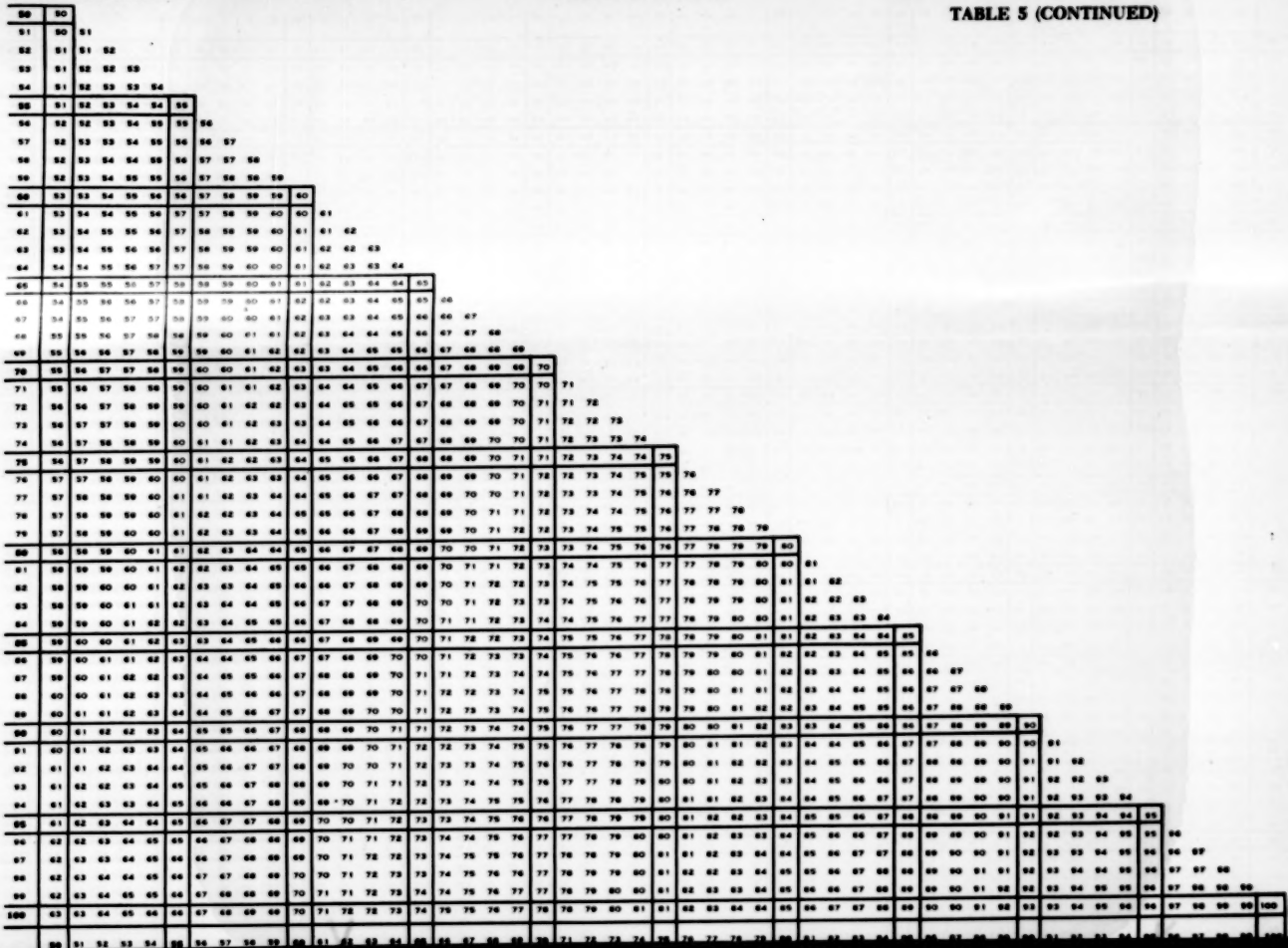
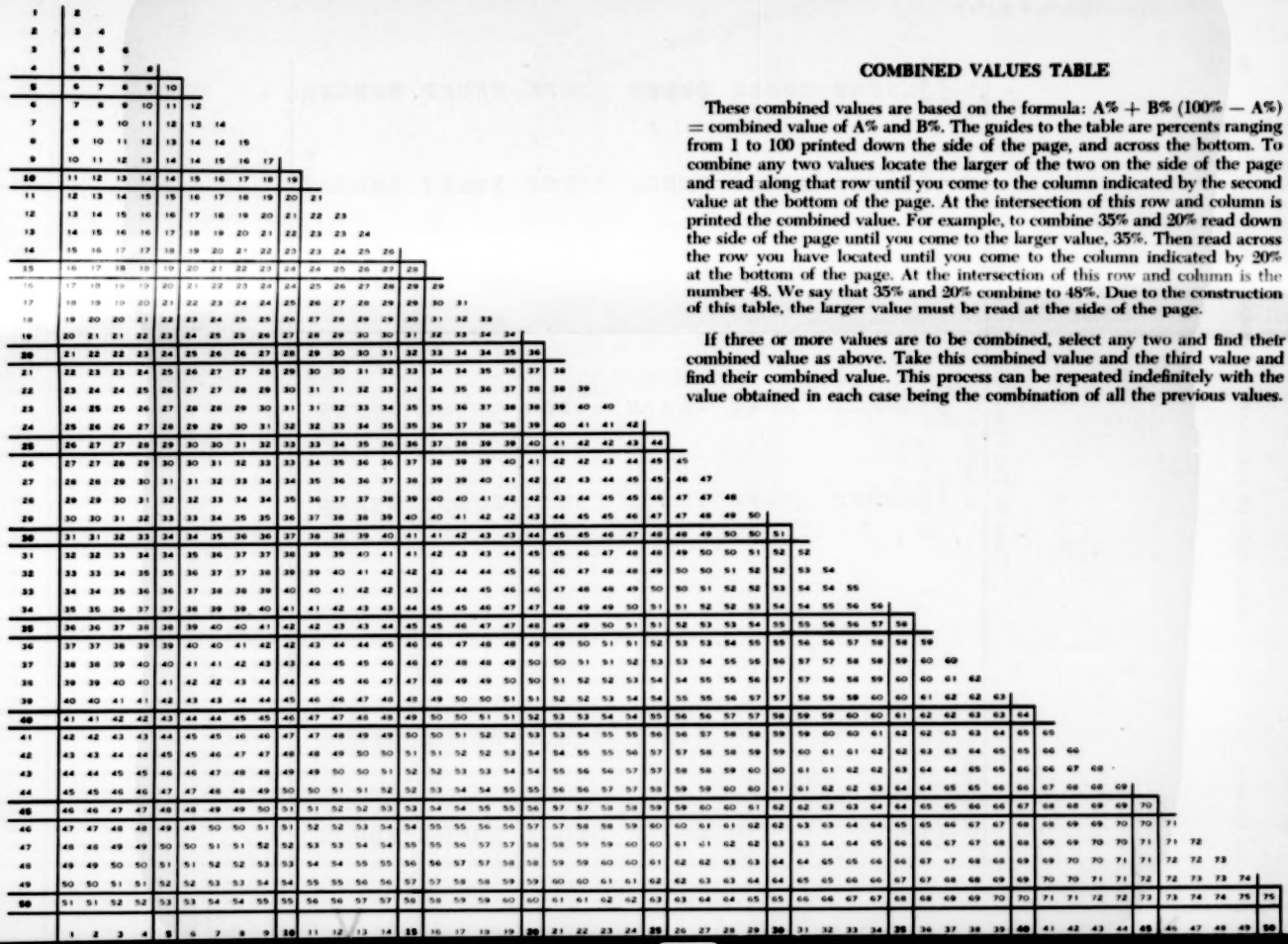
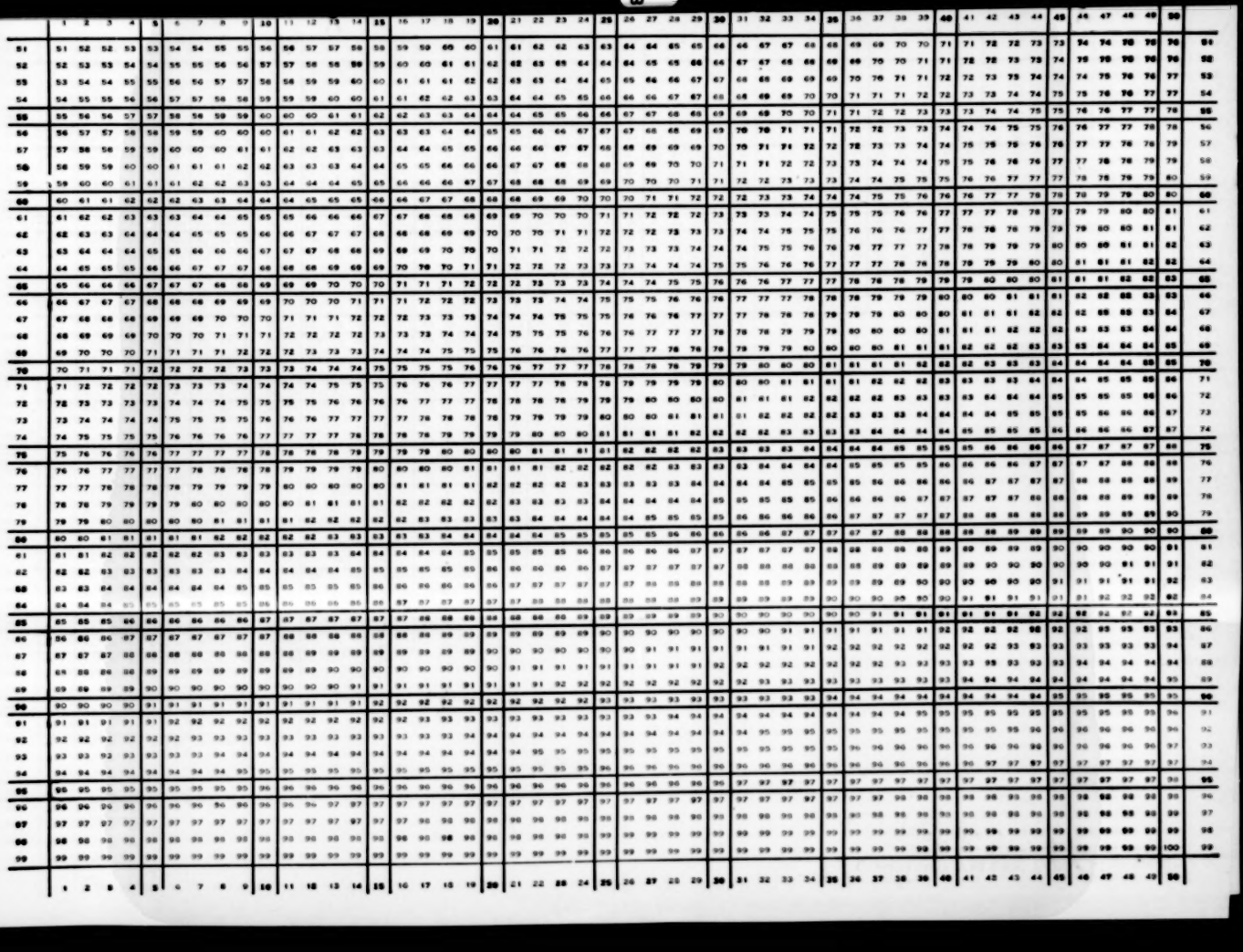
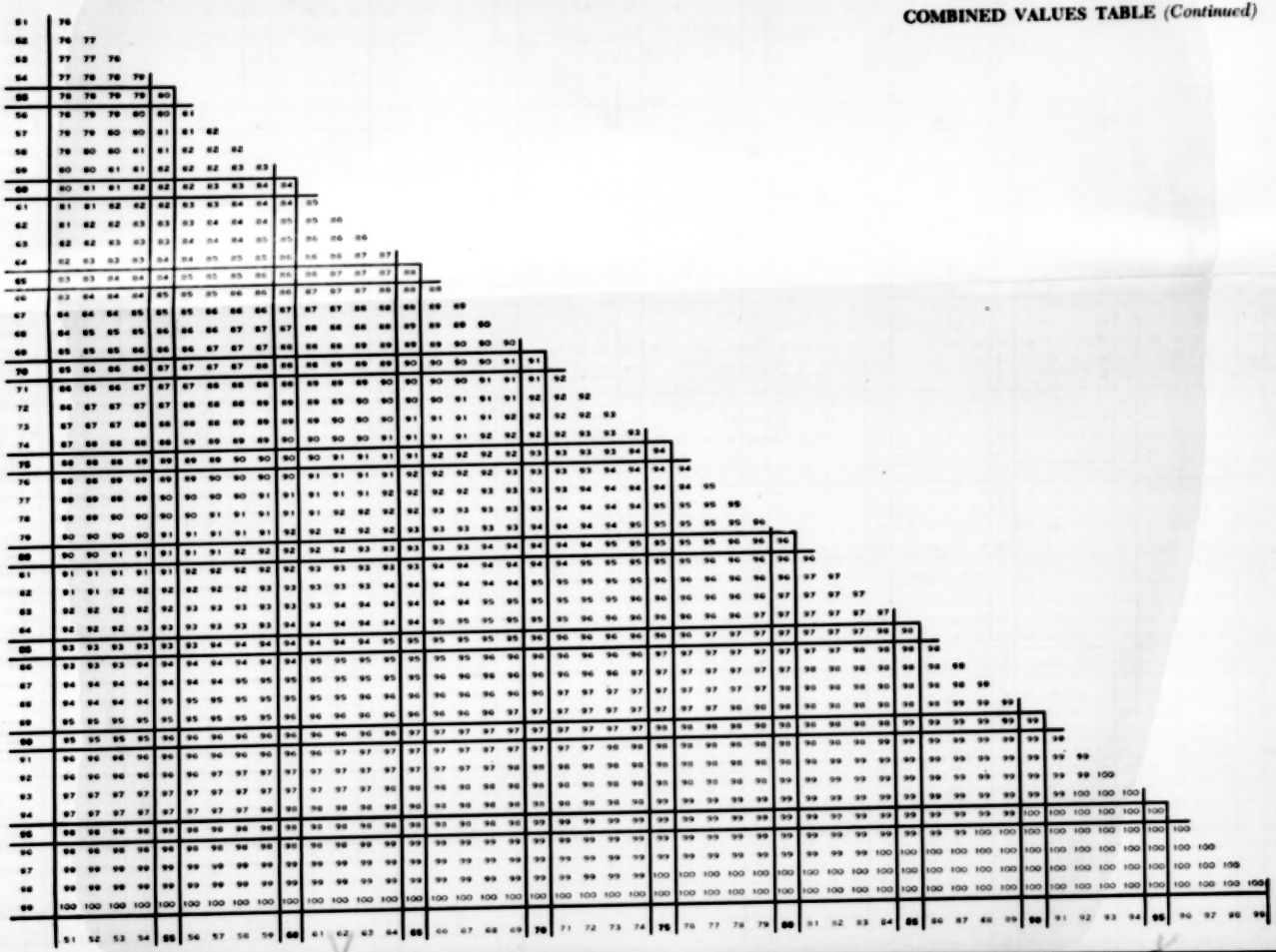


TABLE 6.—*The Visual System*

Impairment of		Impairment of		Impairment of	
Visual System, %	Whole Man, %	Visual System, %	Whole Man, %	Visual System, %	Whole Man, %
0	0	30	28	60	57
1	1	31	29	61	58
2	2	32	30	62	59
3	3	33	31	63	59
4	4	34	32	64	60
5	5	35	33	65	61
6	6	36	34	66	62
7	7	37	35	67	63
8	8	38	36	68	64
9	8	39	37	69	65
10	9	40	38	70	66
11	10	41	39	71	67
12	11	42	40	72	68
13	12	43	41	73	69
14	13	44	42	74	70
15	14	45	42	75	71
16	15	46	43	76	72
17	16	47	44	77	73
18	17	48	45	78	74
19	18	49	46	79	75
20	19	50	47	80	76
21	20	51	48	81	76
22	21	52	49	82	77
23	22	53	50	83	78
24	23	54	51	84	79
25	24	55	52	85	80
26	25	56	53	86	81
27	25	57	54	87	82
28	26	58	55	88	83
29	27	59	56	89	84
				90-100	85

COMBINED VALUES TABLE

These combined values are based on the formula: A% + B% (100% − A%) = combined value of A% and B%. The guides to the table are percents ranging from 1 to 100 printed down the side of the page, and across the bottom. To combine any two values locate the larger of the two on the side of the page and read along that row until you come to the column indicated by the second value at the bottom of the page. At the intersection of this row and column is printed the combined value. For example, to combine 35% and 20% read down the side of the page until you come to the larger value, 35%. Then read across the row you have located until you come to the column indicated by 20% at the bottom of the page. At the intersection of this row and column is the number 48. We say that 35% and 20% combine to 48%. Due to the construction of this table, the larger value must be read at the side of the page.

If three or more values are to be combined, select any two and find their combined value as above. Take this combined value and the third value and find their combined value. This process can be repeated indefinitely with the value obtained in each case being the combination of all the previous values.